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THE GENETIC FACTOR IN ESSENTIAL HYPERTENSION *

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IT has long been suspected that inheritance is concerned in the pathogenesis of essential hypertension because of the frequency with which a history of death from stroke or heart disease in close relatives is obtained. One of the most important attempts to detect whether a genetic factor was concerned and to identify it was that of Weitz [1] of Tubingen in 1923. Weitz made a careful study of 82 patients with hypertension attending the polyclinic. Accepting death from a stroke or heart disease as evidence of hypertension, he found that 76.8% of his patients with hypertension had a positive family history, as compared with 30.3% of 267 controls over 44 years attending the clinic for complaints other than cardiovascular. He noted that the average age of death was earlier in the parents of hypertensives than in the parents of controls. He next proceeded to measure the blood pressure in 93 brothers and sisters of 42 patients with hypertension, and found that the incidence of hypertension was greater than in a control sample of similar age. He noted that in both groups the incidence of hypertension rose with age. It therefore seemed to him that hypertension was a condition which displayed itself as age advanced, and might display itself at different ages in different families. For these reasons he restricted his further enquiry to brothers and sisters born before the patients, because, on such reasoning, they should already have developed the disease if they were going to do so. Of 47 older siblings, the ratio of those without to those with hypertension was 27 to 20, if 150 were taken as the dividing line; 29 to 18, if 160 were accepted. Among the siblings born before the patients, 11 had died of heart disease or stroke. Had these lived, they would probably have been examined and found to have hypertension. Thus, the ratio of those with to those without hypertension approached 1 to 1,

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and this suggested Mendelian dominant inheritance, a conclusion supported by the appearance of the disease in three generations. Weitz investigated other alleged causes of essential hypertension: tobacco, alcohol and physical work, but found no evidence for any. He found the blood pressures of patients with long standing psychic affections no higher than in controls of the same age. He therefore concluded that the disease essential hypertension was inherited as a Mendelian dominant, and that exogenous factors played no part in its pathogenesis but were important only in bringing the patient to the doctor.

Since Weitz's paper, many others have confirmed his findings, indicating that a genetic factor is concerned in the etiology of essential hypertension, Ayman [2] of Boston and Barnes and Browne [3] of London providing particularly important evidence because of blood pressure readings on controls. Allan [4] in the United States, Platt [5] in the United Kingdom, and Sobye [6] in Denmark likewise concluded that the basis of the inheritance was a gene behaving as a Mendelian dominant.

The importance of this subject needs no stressing to an informed audience such as this. After all, our ability to prevent and control disease depends on our knowledge of the genetic and environmental factors concerned. Moreover, should the agent responsible for essential hypertension be carried in a gene obeying the laws of Mendelian inheritance, it would greatly narrow the field in which it would be profitable to seek the basic circulatory fault. Looked at from the angle of the epidemiologist, practicing physician, physiologist or biochemist, the problem is clearly of the first importance. Can we accept that the genetic basis is established?

Looking at the evidence critically, we find that family history studies provide evidence for the inheritance not of high blood pressure but of vascular disease. Deaths from stroke and heart disease are at least in part determined by degenerative vascular disease which, as is well known, may occur with a low as well as a high pressure. Moreover, about a third of the patients with essential hypertension die of a disease unconnected with the high pressure. Measurements of pressures on relatives provide strong evidence for a genetic factor. But when we come to consider the mode of inheritance, we find ourselves face to face with two major issues: first, there are no adequate control studies of relatives of subjects without hypertension; second, all previous studies have been based on a division of subjects into normal and pathologic about some arbitrarily selected value. As we shall see, it is possible, in the population at large, to get any desired ratio between "normal" and "abnormal" by choosing an appropriate age range and an appropriate dividing line between normal and abnormal arterial pressures. In fact, the conclusions reached depend not so much on the data as on the assumptions made in interpreting them.

These considerations seemed so cogent that Drs. Hamilton, Roberts and Sowry and I decided to look at the question again.[7, 8, 9, 10] We made a single

measurement of casual arterial pressure in each individual belonging to the following three groups: (a) 2,031 men and women representing a sample of the general population; (b) 373 first degree relatives of 102 subjects without hypertension (control relatives); and (c) 376 relatives of 109 subjects with essential hypertension (hypertensive relatives). The population sample comprised outpatients attending clinics not known to be associated with alterations in blood pressure; they were all measured in the outpatient waiting hall. The relatives' blood pressures were measured under more various conditions, but the conditions were similar in the two groups.

These measurements established the following points:

1. In the general population at any age, arterial pressure shows a distribution curve of the usual type, except that it tends to be positively skewed. There is no evidence of two populations so far as blood pressure is concerned, and any division between normal and abnormal is purely arbitrary.[7]
2. Blood pressure tends to rise with age, and more in some subjects than in others.[7]
3. The relationship of blood pressure to age is different in males and females.[7]
4. There is no significant difference between the blood pressures of control relatives and the population sample. Thus the method of investigating relatives introduces no important error.[10]
5. At every age, from the second to the eighth decade, the blood pressure of hypertensive relatives tended to be higher than that of the other two groups.[10]

These results made two points abundantly clear: (1) that the conclusions of previous workers concerning the probable role of a genetic factor were almost certainly correct; (2) that the inference of Mendelian dominant inheritance was probably the result of an artefact, namely, the establishment of an arbitrary division between so-called normal and abnormal, and the choice for this division of a value reached by about half the population at the older ages.

It was clear that, to investigate the genetic basis of the condition, it would be necessary to work in terms of blood pressure rather than in arbitrary terms like normality and hypertension. The difficulties were obvious: a considerable variation at any age, and a change with age and sex. Now, these difficulties are not unknown to biometricians, and my colleague, Dr. Fraser Roberts, had met a similar problem in trying to allow for the effects of age and sex on intelligence tests in children. The device adopted was an age-and-sex-adjusted score, by which a value is assigned to each individual which indicates the extent to which he or she deviates from the norm.[8] The values for the norms were taken from the fitted curves relating systolic and diastolic pressures to age in the population sample. The first step is to

calculate the extent to which the observed pressure deviates from the norm for that sex at that age. The next step is to correct these deviations for the variability of blood pressure; the distribution curves are much narrower in the young than in older people, and hence a given deviation from the norm is of greater significance in the young than in the old. Here again, curves were fitted relating variance of pressure to age. Fortunately, the curves for the two sexes crossed at 60. By correcting the variance to age 60, we were thus able to eliminate the effects of sex, so that a single score should correct for both age and sex. To correct for variations, the deviations from the norm were multiplied by the ratio:

$$\frac{\text{standard deviation of arterial pressure at age 60}}{\text{standard deviation of arterial pressure at observed age}}$$

To exemplify, we may calculate the score for an observed systolic pressure of 150 mm. Hg at age 20 and age 60 in women. At age 20 the expected norm is 115 mm. Hg, the deviation thus being + 35; this multiplied by 2.453, the factor correcting for variance, yields + 85, the final score. At age 60 the norm is 155, the deviation — 5, and the multiplier 1.0, the final score thus being — 5. The following table illustrates the way in which scores are related to blood pressure and age.

Age-Adjusted Scores Calculated for Three Arterial Pressures at Age 20 and Age 60 in Females

Observed Blood Pressure		Age-Adjusted Scores (Female)			
		Age 20		Age 60	
S.	D.	S.	D.	S.	D.
120	80	+ 10	+ 20	−35	−10
150	100	+ 85	+ 55	− 5	+10
250	150	+330	+150	+95	+60

It is quite beyond the scope of this paper to discuss the meaning of these scores, but expressing, as they do, the extent to which the arterial pressure departs from the norm, they are perhaps the best expression of the tendency towards an unusually high or low arterial pressure; they express what is commonly called the degree of hypertension or hypotension, as the case may be.

We therefore calculated the age-adjusted scores for all our control and hypertensive relatives and their propositi.* We also calculated these scores for the hypertensive relatives collected by Sobye [6] in Denmark in a way identical with ours. It was satisfactory to find that, with unimportant exceptions, each class of hypertensive relatives gave similar scores in Sobye's

* Propositus (plural, propositi) is the individual from whom the genetic investigation begins.

series and in our own. We were thus able to use the data from his collection to add to our own. Using these scores, we found [10] the same values for parents, siblings and offspring, and no evidence of sex linkage. We were thus able to pool all the scores for first degree relatives and compare these relatives with their propositi. Doing so revealed that, if we arranged propositi in groups of increasing score, the mean scores of relatives rose parallel to those of propositi, until propositi with very high scores were reached, when the scores of relatives fell. We had suspected from our distribution curves that the difference between normal blood pressure and essential hypertension was quantitative, not qualitative. Here we had an extension of this idea. For it seemed that there were degrees of hypertension faithfully reflected in their relatives. It has been noted that the highest degrees of hypertension were not reflected in their relatives. Those subjects with very high scores were all young people with gross hypertension, and the suggestion at once arises that in them hypertension was due to the operation of a different factor or factors, and was in fact "secondary" rather than "primary." We did our best to exclude pyelonephritis and other known examples of secondary hypertension, but we cannot yet be certain that we were successful in doing so. The reassessment of those patients with very high scores is one of the tasks that still await me.

This aspect of our problem was approached in another way. In selecting our propositi we had omitted to consider age. Arranging our propositi in age groups showed that, as age rose, the mean scores of propositi fell; so, however, did the scores of their relatives. Whichever way we looked at it, it seemed that in the hypertensive range, at least, blood pressure behaved as a graded characteristic as far as inheritance is concerned.

To estimate the size of the genetic factor we calculated the regression coefficients of first degree relatives on their propositi and of siblings on siblings. In the hypertensive series, however we set about this problem we received the same kind of answer, namely, a regression coefficient of about 0.2.[10] This means that, if the blood pressure of one member of a family deviates from the norm by plus 10 mm., the first degree relatives will deviate plus 2 mm. on an average. In the control series we received quite equivocal answers, the regression coefficient not being significantly different from zero on the one hand and 0.2 on the other, but the total numbers of subjects we had to deal with were much smaller in the control series.

Our investigations thus showed: first, that there are grounds for believing that a genetic factor is concerned in the pathogenesis of essential hypertension; second, that the difference between normal and high blood pressure is probably quantitative, not qualitative; third, that in the upper ranges, at least, blood pressure is inherited as a graded characteristic; fourth, that the basis of inheritance is therefore probably multifactorial; and, fifth, that the contribution of inheritance is relatively modest, expressed by a regression coefficient of a little more than 0.2.

The major doubt left by these investigations was as to whether the nature and size of the genetic factor were the same in the lower as in the upper ranges of arterial pressure. While it seemed clear that the differences within the hypertensive range were quantitative, we could not be certain that there was not some qualitative difference between genetic behavior in the upper and lower ranges of blood pressure. This doubt has now been resolved by Miall and Oldham,[11] who made an investigation exactly similar to ours except that they selected their propositi without regard for blood pressure, taking a one-in-90 sample of the population of a Welsh mining valley (Rhondda Fach) as propositi. They found that a single regression would describe the dependence of relatives on all kinds of propositi of either sex. The regression coefficient had a value of 0.239. They found no evidence to suggest a deviation from linearity in this regression. The relationship between the systolic pressures of all first-degree relatives and those of their propositi is therefore independent of the level of the blood pressure of the propositi.

The close agreement for the degree of familial resemblance obtained by Miall and Oldham in families derived from a truly random selection of propositi, and ourselves from propositi with so-called essential hypertension, provides strong evidence for the view that blood pressure is inherited as a graded characteristic over the whole range of pressures ordinarily encountered, and that there is no qualitative difference between so-called essential hypertension and normality.

To get these conclusions in perspective it may be said that, in its mode of inheritance, blood pressure resembles height, but that the size of the genetic factor is greater in the case of height. However, the regression coefficient certainly underestimates the size of the genetic factor, since we have been unable to allow for the day-to-day variability of blood pressure, and we have had to allow for the effects of age by a device which is probably valid when it is applied to large numbers, but not so accurate for individuals. By contrast, height shows quite insignificant variations from day to day and, for a considerable span of adult existence, is uninfluenced by age. The difference between the size of the genetic factor in blood pressure and height is probably less than regression coefficients suggest. Even so, it would seem justifiable to conclude that environmental factors are more important than hereditary factors in the pathogenesis of hypertension.[12]

These considerations lead to one further idea, which is so revolutionary that I merely lay it before you, knowing that your minds must instinctively reject it, namely, that the current concept of essential hypertension as a specific disease entity is largely an artefact. I venture to suggest that a restatement of the facts would define essential hypertensives as that group of the population with arterial pressures exceeding a certain value arbitrarily selected and in whom no specific cause can be detected to account for the high pressure. It is suggested that the factors causing it are factors

operating generally on the population. Of these factors, the contributions of age, sex and inheritance can be defined approximately. The influence of environmental factors, which would seem by exclusion to be of great importance, remains to be explored.

Summario in Interlingua

Le ben-cognoscite facto que morbo cardiovascular hypertensive tende a occurrer in distribution familial insimul con le practica de distinguer nettemente inter pression normal e hypertension ha occasionate le hypothese que hypertension essential representa le effecto de un sol gen de acquisition hereditari como dominante mendelian. A fin de examinar le validitate de iste hypothese nos ha executate mesurationes del pression sanguinee in (1) 2.031 homines e feminas como representantes del population general, (2) 373 parentes de prime grado de 102 individuos sin hypertension (parentes de controlo), e (3) 376 parentes de prime grado de 109 individuos con hypertension essential (parentes hypertensive). Le mesuration esseva executate un sol vice pro cata individuo; le tempore del mesuration esseva accidental. Inter le representantes del population general, le pression sanguinee monstrava continue variationes in cata decade de etate; le valores median e etiam le dispersion supra e infra le valores median montava con le etate. Le parentes de controlo monstrava simile conditiones. In ambe iste gruppos normal, plus que 50 pro cento del individuos de etates plus avantiate monstrava "anormalmente" alte valores systolic. Le curvas de distribution in le gruppo del parentes hypertensive exhibiva simile formas, sed illos esseva plus alte pro omne etates ab le secunde al octave decade. Le analyse statistic monstrava que le ratas del augmento de pression sanguinee in le curso del vita esseva le mesme in parentes hypertensive que in le resto del population; le analyse etiam confirmava que le pression sanguinee del parentes hypertensive tendeva a esser plus alte a omne nivellos de etate.

Pro resolver le problema del analyse genetic, nos elaborava un systema computative que neutralisava le observate effectos de etate e sexo super le pression sanguinee. Per medio de iste systema il esseva possibile monstrar que plus alte grados de hypertension in un gruppo de individuos corresponde a plus alte grados de hypertension inter lor parentes. Assi, alte pression sanguinee pare esser hereditari como characteristica graduate como, per exemplo, altor de statura. In le region de "hypertensivitate," le grado de similaritate inter parentes primari es exprimite per un coefficiente correlational de levemente plus que 0,2. Isto significa que cata 10 mm Hg de deviation ab le norma del pression sanguinee corresponde, como regula median, a un simile deviation de 2 mm Hg in fratres, sorores, patres, matres, e infantes. Miall e Oldham ha demonstrate recentemente que iste modo e iste grado de hereditate vale a transverso le integre spectro del pressiones arterial. Assi, considerate ab le puncto de vista del hereditate, le differentia inter normal pressiones sanguinee e hypertension essential es quantitative e non qualitative.

Iste observationes pare indicar (1) que pression sanguinee es hereditabile como characteristica graduate, (2) que le conceptos de normal e alte pressiones sanguinee es artefactos (de maniera que le notion del hereditate de hypertension essential como dominante mendelian appare etiam como basate super un artefacto, (3) que le principio de hereditate es responsabile pro solmente un parte—probabilemente minus que un medietate—del variabilitate del pression sanguinee, e (4) que le ambiente es possibilemente un plus importante factor que le hereditate, specialmente in determinar le progresso del augmento que occurre in le pression sanguinee con avantiamento de etate.

BIBLIOGRAPHY

1. Weitz, W.: Zur Ätiologie der genuinen oder vasculären Hypertension, Ztschr. f. klin. Med. **96**: 151, 1923.
2. Ayman, D.: Heredity in arteriolar (essential) hypertension: a clinical study of the blood pressure of 1,524 members of 277 families, Arch. Int. Med. **53**: 792, 1934.
3. Barnes, J., and Browne, F. J.: Blood pressure and the incidence of hypertension in nulliparous and parous women in relation to the remote prognosis of the toxaemias of pregnancy, J. Obst. and Gynaec., Brit. Emp. **52**: 1, 1945.
4. Allan, W.: Heredity in hypertension: statistical study, Arch. Int. Med. **52**: 954, 1933.
5. Platt, R.: Heredity in hypertension, Quart. J. Med. **16**: 111, 1947.
6. Sobye, P.: Heredity in essential hypertension and nephrosclerosis. A genetic-clinical study of 200 propositi suffering from nephrosclerosis, Op. dom. Biol. hered. hum. Kbh. **16**: 1948, Munksgaard, Copenhagen.
7. Hamilton, M., Pickering, G. W., Roberts, J. A. F., and Sowry, G. S. C.: The aetiology of essential hypertension. 1. The arterial pressure in the general population, Clin. Sc. **13**: 11, 1954a.
8. Hamilton, M., Pickering, G. W., Roberts, J. A. F., and Sowry, G. S. C.: The aetiology of essential hypertension. 2. The scores for arterial blood pressures adjusted for differences in age and sex, Clin. Sc. **13**: 37, 1954b.
9. Pickering, G. W., Roberts, J. A. F., and Sowry, G. S. C.: The aetiology of essential hypertension. 3. The effect of correcting for arm circumference on the growth rate of arterial pressure with age, Clin. Sc. **13**: 267, 1954.
10. Hamilton, M., Pickering, G. W., Roberts, J. A. F., and Sowry, G. S. C.: The aetiology of essential hypertension. 4. The role of inheritance, Clin. Sc. **13**: 273, 1954c.
11. Miall, W. B., and Oldham, P. D.: Unpublished observations.
12. Pickering, G. W.: High blood pressure, 1955, Grune & Stratton, New York.

DEFECTIVE SERUM GAMMA GLOBULIN FORMATION *

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THE anomaly called agammaglobulinemia has become a fairly well known clinical entity, although prior to Bruton's report [1] in 1952 it had never been described. The subject of his study was an eight year old boy who for four years had had a continuous series of bacterial and viral infections. Electrophoretic studies of the serum proteins led to the surprising discovery of complete absence of the gamma fraction in an otherwise normal serum protein pattern. Immunologic studies disclosed the complete lack of antibodies, including isohemagglutinins, and repeated challenge with a number of antigens failed to evoke an antibody response.

Since then other similar cases have been discovered. Most of them have been young boys,[2, 3, 4, 5] but one [6] was a baby girl, and a few have been adults, three of them women.[7, 8, 9] In all of these, the pattern has been quite consistent. The remarkable susceptibility to infections and the absence of demonstrable antibodies have been characteristic.

The present report concerns experiences with seven patients in whom gamma globulin was not demonstrable electrophoretically. Six of them were adults when the anomaly was discovered, although in two of them the manifestations began during childhood. The seventh is a boy, now 12 years old, who was originally reported by Stern and Reiner [10] in 1947.

The clinical manifestations of the anomaly vary considerably in this series, and the cases fall roughly into three categories. Those in the first group, like the cases cited, possess no antibodies and are subject to repeated infections, and there is no apparent underlying disease. Those in the second group likewise appear to have no underlying systemic disease, but isohemagglutinins are present, at least in low titer, and infections are not unusually frequent, even though other circulating antibodies are evidently produced in but very small quantity. In the third group are those that possess an associated systemic disease which might be regarded as either primary to or concomitant with the globulin defect. These patients possessed isohemagglutinins as well as certain fixed tissue antibodies, but were subject to infection.

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Case Reports

The following three cases are examples of the first group.*

Case 1. A 37 year old white man had been perfectly well until 1943 when, while on active duty in the Navy, he developed what was diagnosed as virus pneumonia. He was hospitalized for about six weeks and recovered. From then on, however, there was a continuous series of infections, requiring seven hospitalizations in the next two and one-half years.

He came under our observation in March, 1947, when he was admitted for acute otitis media. He had recently recovered from an indolent, protracted attack of hepatitis lasting about six months. There were several subsequent admissions during 1947 for sinusitis, otitis, and colitis presumably due to *Giardia lamblia.* In November, 1947, he was hospitalized for acute bronchitis with a fever of 102° F. At this time determination of the plasma protein concentration disclosed a total protein of 6.2 gm. per 100 c.c., with 5.1 gm. of albumin and 1.1 gm. of globulin. A second determination yielded an albumin level of 5.2 gm. and globulin of 0.6 gm. per 100 c.c. Electrophoretic analysis revealed a normal plasma protein pattern with the exception of the absence of gamma globulin (figure 1).

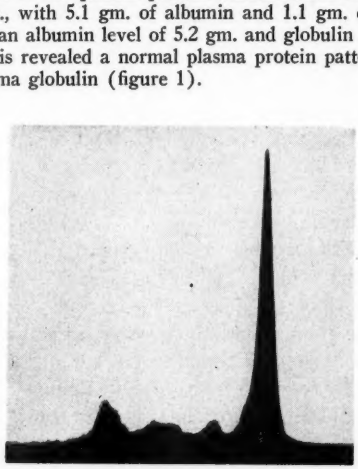


Fig. 1. Electrophoretic pattern in case 1.

In April, 1948, the patient was admitted with pneumonia. The response to penicillin was prompt, but on cessation of penicillin a relapse occurred in which type 16 pneumococcus was recovered from the sputum. Recovery was prompt and sustained with a more protracted course of penicillin.

In July, 1948, he entered the hospital with fever, joint pains, rash, enlarged lymph nodes and spleen. The leukocyte count was 5,700, with 53% lymphocytes, many of which were characteristic of those seen in infectious mononucleosis. The heterophil antibody determination was negative, however.

The patient was thereafter given infusions of human irradiated plasma, 500 c.c. every two weeks for a period of three months. With this his susceptibility to infections seemed to decrease. He returned in January, 1949, however, with acute sinusitis and bronchitis. In May, 1949, he developed hydrarthrosis of the left knee without fever. This subsided in the course of four weeks and never returned.

* The electrophoretic analyses were performed in a barbital buffer at a pH of 8.6 using schlieren scanning in a Klett Tiselius electrophoresis apparatus.

In July and August another series of plasma infusions was given, with apparent benefit. However, in September he developed a second attack of hepatitis which was considered to be of the homologous serum variety contracted from the plasma infusions.

The respiratory infections continued until March, 1950, when gamma globulin was given in doses of 20 c.c. intramuscularly weekly. This appeared to be quite effective, his next hospitalization occurring a year later for acute bronchitis. The effectiveness of the gamma globulin in this dosage appeared to abate, however, and almost continuous respiratory infection with exacerbations has been present since. In February, 1954, a large dose of 120 c.c. (19.2 gm.) of gamma globulin was given in an effort to determine whether specific antibodies could be elaborated in response to an antigen if gamma globulin was present. Typhoid vaccine was used as the antigen. No antibody response was observed, but for the next three months the patient was more nearly free of respiratory infections than he had been in several years.

A great variety of laboratory examinations has been performed in an effort to detect underlying disease as well as to shed light on the nature of the anomaly.

Renal function studies have always been normal, with the exception of small amounts of albumin during febrile episodes.

Hematologic studies, including sternal marrow examination, have been consistently normal except for leukocytosis during acute infections and the appearance of atypical lymphocytes in an episode of what was thought to be infectious mononucleosis. The sedimentation rate has been consistently low—0.5 to 2 mm. even during infections.

Liver function tests were completely normal except during episodes of hepatitis. Liver biopsy likewise was normal.

Tests of adrenal cortical function, including the eosinophil response to epinephrine and ACTH, sweat sodium determination, and 17-ketosteroid excretion were all normal.

Histologic examination of an enlarged axillary lymph node (figure 2) resulted in the diagnosis of marked follicular hyperplasia, although giant follicular lymphoblastoma was seriously considered.

Studies of thyroid function, including the protein-bound iodine determinations, radioiodine uptake and thyroxin synthesis, were normal.

Immunologic studies, including intradermal tests for diphtheria (Schick), scarlet fever (Dick), histoplasmosis, tuberculosis, coccidioidomycosis, brucellosis, and a large number of allergens, all indicated absence of antibody.

Agglutination tests, including typhoid, paratyphoid A and B, brucellosis, Weil-Felix, tularemia, heterophil antibody, cold agglutinins and isohemagglutinins, were all negative. The patient's red blood cells were group B, but his serum contained no anti-A agglutinins.

Several efforts to stimulate antibody production with typhoid vaccine, with and without exogenous gamma globulin, were unsuccessful in producing agglutinins. One interesting sidelight was that typhoid vaccine ordinarily produced no reaction whatever, local or systemic. However, after the patient had been given a large quantity of gamma globulin, both a local and a systemic reaction occurred. This response to typhoid inoculation disappeared after a month.

In the past year evidences of advanced liver disease have become apparent, with marked weight loss, persistent ascites and falling serum albumin.

Case 2. A 17 year old boy was admitted to Los Angeles County General Hospital March 3, 1954, because of shortness of breath, cough and weight loss since an attack of pneumonia three months before.

He had been perfectly well, except for measles, mumps, chickenpox and whooping cough, from which he recovered normally, until 1947 when, at the age of 10 years, he developed a long continued fever which remained undiagnosed. During the course

of this illness cervical lymph node enlargement occurred, and the diagnosis of Hodgkin's paragranuloma was made on histologic study of one of the nodes. Enlargement of the spleen was discovered in early 1949 and a second cervical lymph node biopsy was performed (figure 3). The diagnosis of giant follicular lymphoblastoma was made this time. Subsequent independent study of the sections by several competent pathologists resulted in a unanimous agreement on the diagnosis of benign hyperplasia. No specific therapy was given because the patient was asymptomatic. At this time the tuberculin test was negative to 0.01 and 0.1 mg. Chest x-ray showed "fluffy infiltration in both lungs, greater at the bases."

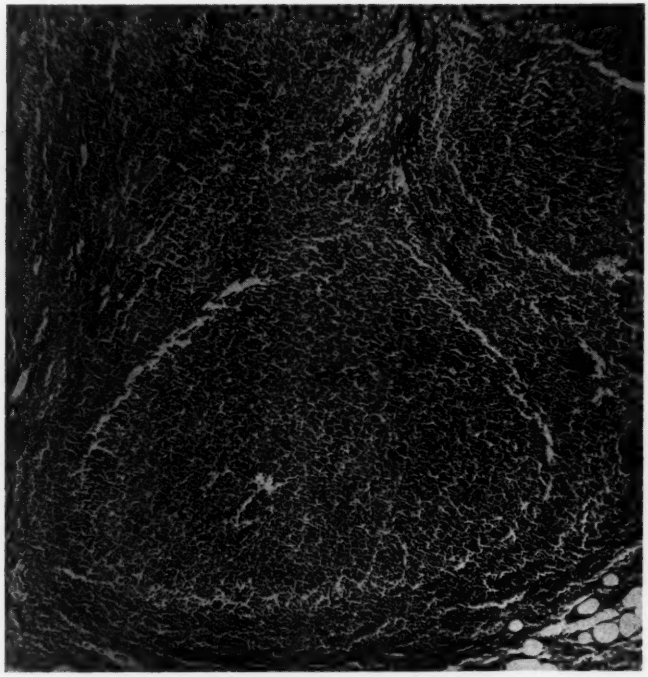


FIG. 2. Histologic appearance of axillary lymph node from case 1. (× 100.)

In 1950 he was admitted to another hospital with pneumococcus meningitis, from which he recovered slowly. Subsequently a right mastoidectomy was performed because of resistant infection. A left mastoidectomy was performed three years later for the same reason.

Eight months before admission the maxillary sinuses were drained surgically. Throughout this whole period there had been a persistent upper respiratory infection, with acute episodes of sinusitis, bronchitis and pneumonia. During the year prior to admission there had been a painless swelling of both knee joints.

Three months before admission he had been hospitalized for pneumonia and treated with antibiotics. He recovered from the acute phase but since then has had

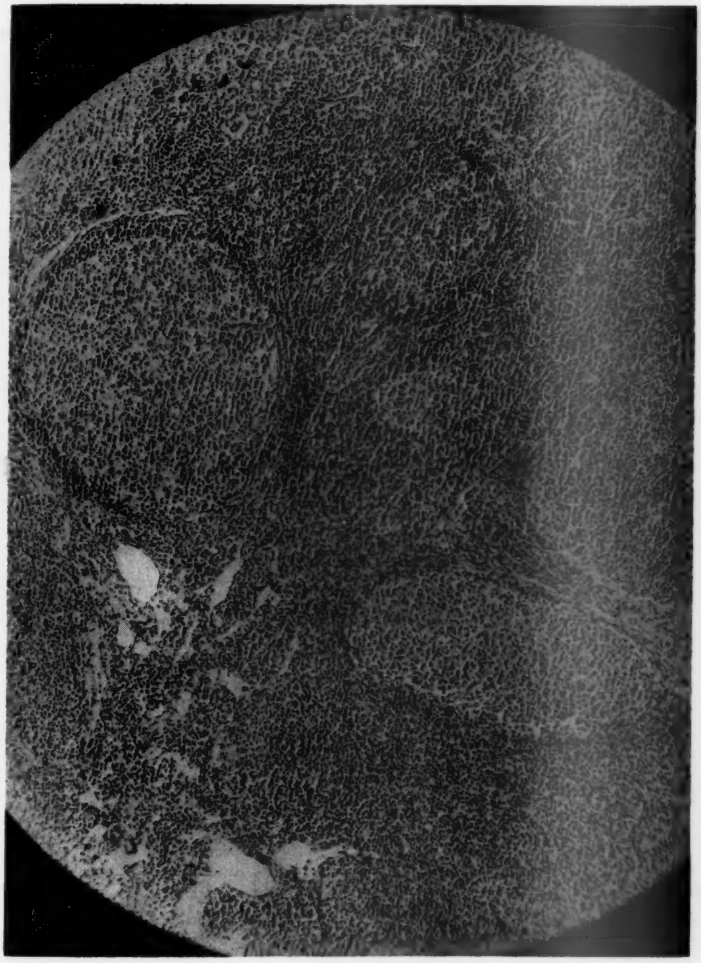


FIG. 3. Section of axillary lymph node from case 2. (×75.)

a productive cough, some shortness of breath, a low grade fever, and loss of 10 pounds.

On examination the patient was small and underdeveloped for his age. His weight was 76 pounds. The temperature was 97° F.; respirations, 30 per minute; blood pressure, 110/65 mm. Hg. The hearing was impaired in both ears, and the right external auditory canal contained purulent material. Cervical and axillary lymph nodes were small, firm and discrete. The lungs were resonant, but there were numerous moist râles scattered throughout both lungs, predominantly in the right

lower chest. The heart tones were normal and no murmurs were audible. The spleen was easily palpable, extending 8 cm. below the costal margin. The liver was not palpable. Bilateral hydrarthrosis of the knee was present.

The urinalysis was completely normal. The red blood count was 6.00 million; hemoglobin, 14.9 gm. per 100 c.c.; white cell count, 14,600, with 77% polymorphonuclear leukocytes, 2% eosinophils, 18% lymphocytes and 3% monocytes. No abnormality of the red or white cells was detected.

The erythrocyte sedimentation rate was 2 mm. per hour (Wintrobe, uncorrected).

The chest x-ray showed infiltration of the right base and numerous fibrous strands and streaky shadows throughout both lung fields, with a suggestion of cystic areas in the left lower lobe. The conclusion was: "Appearance suggests cystic disease of the lungs with pneumonia in the right lower lobe."

Examination of aspirated sternal bone marrow disclosed "increased red cell mitotic activity and unusual distribution of leukopoietic cells not diagnostic of any specific entity."

Study of the blood for lupus erythematosus cells was negative.

The plasma proteins were 5.2 gm. per 100 c.c., with albumin 4.6 gm. and globulin 0.6. Electrophoretic analysis showed a normal pattern with the exception of a complete absence of gamma globulin (figure 4). Fibrinogen was 0.32 gm. per 100 c.c.

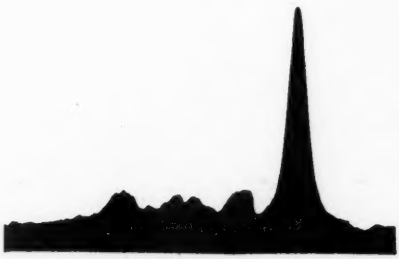


FIG. 4. Electrophoretic pattern in case 2.

The tuberculin test using PPD was negative.

The red blood cell type was A. No agglutinins for type B cells were present in the serum.

The protein-bound iodine was 7.2 micrograms per 100 c.c.

On antibiotic therapy and postural drainage the pulmonary symptoms and signs abated. Aspiration of the joint spaces of the knees produced sterile clear fluid. Injection of Hydrocortone produced no demonstrable improvement.

The patient was given a course of ACTH, 60 mg. per day. Repeated electrophoretic analyses of his plasma proteins over a period of six weeks showed persistent absence of gamma globulin. His general condition improved remarkably, however. He gained 30 pounds in weight, the hydrarthrosis disappeared, and the spleen became impalpable.

A month after discharge the patient returned to the hospital with a severe fulminant pneumonia to which he succumbed after five days, despite the administration of large quantities of gamma globulin and antibiotics. The postmortem examination disclosed marked pulmonary fibrosis, with widespread acute pneumonic process superimposed, and a large spleen with hyperplasia of the reticulum. Nothing to suggest lymphoma was found.

*Case 3.** A 28 year old physician developed bronchiectasis following whooping cough and pneumonia at the age of six years. Throughout childhood and adolescence he had many respiratory infections. In 1950, at the age of 23, a bilateral pulmonary lower lobectomy was performed for the bronchiectasis, during which blood transfusions were administered. After recovery from the operation, a persistent low grade fever with lymphadenopathy and splenomegaly appeared. In 1952 an axillary lymph node was removed for examination, and after considerable debate the diagnosis of giant follicular lymphoblastoma was made (figure 5). Several excellent pathologists felt, however, that the histologic picture was that of a benign follicular hyperplasia. X-ray therapy was applied to the lymph nodes and spleen, with reduction

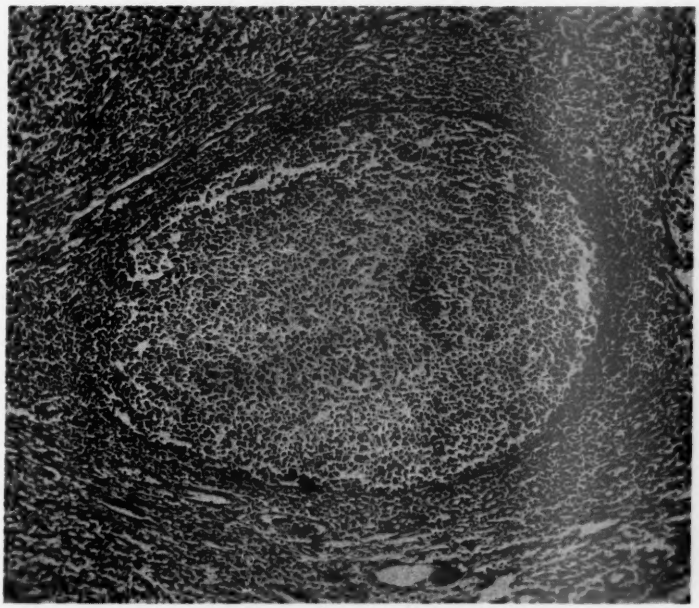


FIG. 5. Section of axillary lymph node from case 3.. (× 100.)

in their size. The spleen promptly returned to its original size, but the lymph nodes have remained small. In 1953 a splenectomy was advised. At surgery a nodular cirrhotic liver was found, and the spleen was not removed. Ascites developed immediately after the operation. The serum proteins at this time were 4.2 gm. of albumin and 0.9 gm. of globulin per 100 c.c. Numerous episodes of respiratory infection ensued. Ascites was reasonably well controlled with sodium limitation. In August, 1954, electrophoretic analysis of the serum proteins disclosed the complete absence of gamma globulin (figure 6). Isohemagglutinins were absent, although the patient's erythrocytes were group O. Since September, 1954, he has been receiving 10 c.c. of gamma globulin every five days and has remained remarkably free of infections.

*To be reported in detail.

Comment: These three cases possess several features in common. They all exhibit the complete pattern of agammaglobulinemia, with absence of antibody production and susceptibility to infection. Of particular interest is the striking splenic and lymph node enlargement leading to the suspicion or diagnosis of giant follicular lymphoblastoma in all three. Although this disease is not absolutely excluded in cases 1 and 3, there is nothing in their courses over the past six and three years, respectively, since the diagnosis was proposed, to indicate a progressive malignant lymphoma. It appears more likely that this remarkable hyperplasia is in some way secondary to the agammaglobulinemia or to the resulting infections.

Two of them have developed advanced liver disease, presumably due to chronic viral hepatitis, possibly of the homologous serum variety. This suggests, at least, that there may be hazard in exposing these patients to the hepatitis virus.

There are two cases in the second group.

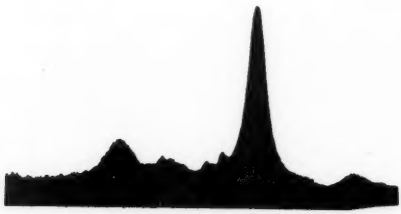


FIG. 6. Electrophoretic pattern in case 3.

Case 4. A 25 year old white male was admitted to the hospital October 12, 1953, because of burning, cramping lower abdominal pain associated with nausea and vomiting of four days' duration. This group of symptoms had occurred in acute episodes since 1949, and the patient had been admitted at least 12 times to other hospitals during this period. Repeated x-rays of the gastrointestinal tract, as well as many other studies, apparently failed to reveal the nature of the syndrome.

The physical examination on admission was quite normal except for diffuse abdominal tenderness. There was no fever. The cardiovascular and neurologic systems were normal, and lymph node enlargement and splenomegaly were not found.

The urinalysis as well as the blood count was normal. The erythrocyte sedimentation rate was 1 mm. per hour (Wintrobe). Appropriate preparations of the blood failed to reveal sickling of the red blood cells. The serum amylase was 44 units per 100 c.c.; the total serum bilirubin, 0.2 mg. per 100 c.c.; and the Bromsulphalein test revealed no dye retention at 45 minutes.

The serologic tests for syphilis were negative. Urinary porphyrins were negative. Stools contained cysts and motile forms of *Giardia lamblia* only. X-ray examinations of the gastrointestinal tract, gall-bladder and sella turcica were normal.

The serum albumin concentration was 4.8 gm. and the serum globulin was 0.9 gm. per 100 c.c. Electrophoretic analysis revealed no gamma globulin (figure 7). The red blood cells were type A, and no demonstrable anti-B agglutinins were detectible by ordinary methods, but a very low titer was demonstrated by the indirect Coombs' test.

Examination of the sternal marrow disclosed the virtual absence of plasma cells.

Tests for agglutinins of typhoid O and H and paratyphoid A antigens were negative. Agglutinins of paratyphoid B were 1 plus in a titer of 1:20. The Weil-Felix test was negative, as was the test for brucella agglutinins. Heterophil antibody and cold agglutinins tests were negative.

Tuberculin, histoplasmin, coccidioidin and brucellergin intradermal tests were negative. However, tests of skin sensitivity to several allergens were positive.

The standard immunizing course of typhoid-paratyphoid produced but a trace of H antigen agglutinin in a 1:10 dilution, although a local reaction at the site of injection occurred.

Tests of adrenal function, including 17-ketosteroid excretion and eosinophil response and uropepsin excretion following the administration of ACTH and epinephrine, were normal.

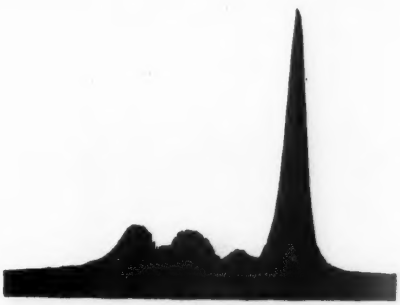


FIG. 7. Electrophoretic pattern in case 4.

The patient continued to have episodes of abdominal pain, during which the abdomen would become quite rigid, with rebound tenderness present. Placebos usually gave complete although temporary relief. Neurologic consultants found no evidence of organic neurologic disease, and electroencephalograms were negative. The psychiatric consultant's diagnosis was "psychotic reaction, unclassified, chronic."

Case 5. A nine year old boy was observed by Stern and Reiner [10] at the age of three years, at which time he had a peculiar undiagnosed episode of edema lasting about one month. There was no evidence of renal disease. The plasma proteins were generally depressed, and gamma globulin was absent electrophoretically. The boy recovered completely and has been well since, with no unusual infections. Although the other plasma protein fractions returned to normal, the absence of gamma globulin has persisted up to the time of his present examination, six years later (figure 8*). This patient's serum possesses isohemagglutinins in high titer.

Comment: Although both of these patients show marked depression of gamma globulin electrophoretically, it is evident that they are able to produce antibodies to some extent at least. Both have isohemagglutinins, and neither is particularly subject to infections. The absence of plasma cells in

* The blood specimen of case 5 was made available for analysis through the kindness of Professor Abraham White.

the marrow of case 4 perhaps provides a clue to the mechanism of the globulin defect.

The third group consists of two cases.

Cases 6 and 7. Two brothers of French descent were 60 and 58 years old, respectively, at the time of their deaths. Both had long histories of upper respiratory infections, bronchitis and pneumonia for which they had been hospitalized many times over the last 25 years of their lives. One brother was found to have chronic lymphocytic leukemia in 1949, and the same disease was found in the other a year later. A third brother, who likewise had had many infections, died in his thirties of leukemia.

In the course of study of their leukemias, electrophoretic analyses of their serum proteins were performed, and gamma globulin was found to be absent in both (figures 9 and 10). Isohemagglutinins were present, however, as were antibodies to tuberculin and several allergens. ACTH administered for their leukemias failed to induce production of detectible amounts of gamma globulin. Both brothers died in 1953, and postmortem examination disclosed the typical pathologic findings of chronic lymphocytic leukemia.

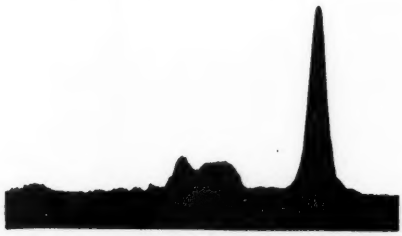


FIG. 8. Electrophoretic pattern in case 5.

Comment: These two cases represent the association of depressed serum gamma globulin and a systemic disease of the reticuloendothelial system. Although some antibodies were evidently present, repeated infections were striking, and antedated by years the appearance of the leukemias.

DISCUSSION

The subjects of this report, although presenting the one common feature of seriously depressed serum gamma globulin, varied somewhat in their clinical manifestations as well as in antibody content. Most of them are obviously deficient and are consequently highly susceptible to all manner of infection. Two cases seem to possess sufficient antibody to provide adequate protection, and cases 6 and 7 have a concomitant disease of the reticuloendothelial system that might be regarded as primary.

Although these seven cases have been rather arbitrarily separated into three categories on the basis of clinical manifestations, it seems quite possible that they all possess the same fundamental defect, varying only in severity.

The pathogenesis of this anomaly is at the moment obscure. It has been proposed that there are two mechanisms,[7] the one operating in young males

being a sex-linked hereditary process, and the other creating the defect in adults of both sexes being acquired through some sort of assault on the gamma globulin-producing function.

Although the latter explanation is suggested by some circumstances, it is difficult to envision a noxious agent which can pick out one specific

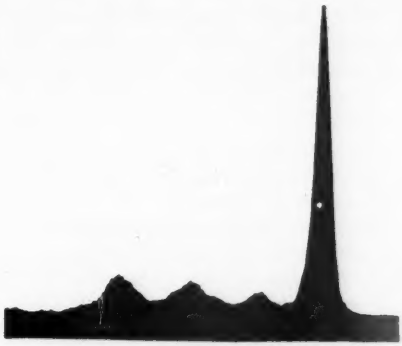


FIG. 9. Electrophoretic pattern in case 6.

function and eliminate it entirely without damaging closely related functions. The elimination of a single protein fraction is much more characteristic of a hereditary process in which the gene for that particular function is defective. Afibrinogenemia and hemophilia are notable examples of this process. The isolated depression of gamma globulin would appear to be a

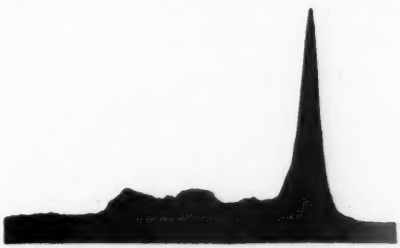


FIG. 10. Electrophoretic pattern in case 7.

similar phenomenon. The fact that the manifestations of the defect may not appear until relatively late is not inconsistent with this hypothesis when it is considered that many inherited diseases make their appearances at widely varying ages in different individuals.

Arends and his associates,[11] in a study of the serum proteins in lymphomatous diseases, describe briefly the case of a middle aged woman in whom

gamma globulin was absent. Her course closely resembled that of our first three patients. The type of lymphoma was not designated, however. Although the absence of gamma globulin was ascribed to the lymphoma, it seems possible that this case represents another instance of intense reticuloendothelial hyperplasia in response to the absence of gamma globulin and its consequences.

Prasad and Koza [7] relate the agammaglobulinemia observed in their patient to a disseminated focal granulomatous process of unidentified nature found in sections of the spleen and liver. It appears equally if not more likely that the granulomatous disease is, on the contrary, secondary to the absence of gamma globulin. Such diseases, as a rule, produce the opposite response: an increase in gamma globulin. Furthermore, it seems unlikely that the total gamma globulin elaborating mechanism could be paralyzed by a focal disorder such as the one described.

It is not too difficult to conceive of the globulin-producing mechanism being deranged by a diffuse disease of the reticuloendothelial system such as lymphatic leukemia. It was at first assumed that this was the case in patients 6 and 7. The fact that evidences of poor antibody response anteceded the appearance of the leukemias by many years in both instances, plus the fact that this globulin defect has not been found in the studies of serum protein of many cases of leukemia by ourselves and others,[12, 13, 14, 15] make this relationship seem unlikely. Wintrobe [16] has one similar case under observation at the present time, however.

It is tempting to conjecture that the agammaglobulinemia may, in fact, be in some way predisposing to the development of the leukemia in these cases.

Although a familial incidence of agammaglobulinemia has been sought, the defect has not been found in more than one member of a family. The two brothers with the leukemia represent the first instance in which a familial incidence has been reported. If further experience fails to indict leukemia as a predisposing factor in agammaglobulinemia, these two cases lend strong support to the hypothesis of inheritance of the disorder.

One of the perplexing aspects of this anomaly is that the whole gamma globulin fraction can be virtually eliminated at once when it is considered that this fraction is composed of a heterogeneous group of globulins with different physical and chemical properties. The simultaneous elimination of the whole fraction must mean that all of the gamma globulin, including antibodies, is elaborated by a single highly specialized tissue, the function of which can be deranged in varying degree.

Although varied pathologic changes have been seen, they all appear to be secondary to repeated or long-standing infections of one type or another. The only suggestion as to where the specific defect might be lies in the observation in a few cases [4] that plasma cells are markedly reduced in the bone marrow. That this is the site of the defect is further supported by the absence of gamma globulin noted occasionally in multiple myeloma,[17] a disease

in which plasma cell function is obviously deranged. More detailed hematologic study may shed further light on the mechanism of this disorder.

The disease is not difficult to recognize, once its clinical features are appreciated. Suspicion of it may be supported by the finding of an unexpectedly slow erythrocyte sedimentation rate, an unusually low total serum globulin concentration, or the absence of isohemagglutinins for opposite red cell types, except, of course, in those patients whose blood type is AB. Electrophoretic analysis of the serum proteins finally proves the diagnosis.

Agammaglobulinemia is obviously not a new disease. Undoubtedly it accounts for the many instances of poor resistance or early death from infection seen in the past. The advent of antibiotics permitting survival and the application of electrophoresis were responsible for its recent discovery. It is probably not a rare disease, either. Very likely many more cases will be discovered in the near future.

The disorder does not appear to be a transitory one, as it is in those instances resulting from malnutrition.[18] Several of our patients have exhibited the clinical effects for many years, with no indication of spontaneous improvement. The predisposition to infection may be ameliorated to some degree, however, by the regular administration of exogenous gamma globulin in adequate amounts and the appropriate use of antibiotics.

Summary

Agammaglobulinemia is now a well established and widely recognized clinical entity. It has been seen most frequently in young boys but has also been observed occasionally in adults, both male and female. The outstanding characteristic of this anomaly is the inability to elaborate gamma globulin, including antibodies, and the consequent marked susceptibility to infections, although all other serum protein fractions are normal.

The present report describes seven cases, all in males. In three of the patients, lymphadenopathy and splenomegaly were prominent features, and the diagnosis of giant follicular lymphoma was either made or seriously entertained on lymph node biopsy in each instance. One of them died, and at postmortem examination no evidence of lymphoma was found. The other two, although still living, show no evidence of progressive lymphomatous disease. Both of these, however, have all the evidences of advanced liver disease as a result of chronic hepatitis.

Two patients, although devoid of serum gamma globulin electrophoretically, possessed isohemagglutinins and were not unusually susceptible to infections. No evidence of underlying or concomitant organic disease was detectible. Plasma cells were markedly diminished in the sternal marrow of one, however. These may represent a milder degree of the same fundamental defect.

The other two cases were brothers, both of whom had long histories of respiratory infections. They developed chronic lymphocytic leukemia late

in life, and subsequently were found to possess no gamma globulin on electrophoretic examination of their serum proteins. This is a very rare finding in leukemia and is probably coincidental rather than a result.

The pathogenesis of agammaglobulinemia is obscure. It has been proposed by others that there are two mechanisms, the one operating in children being hereditary and the one creating the defect in adults being acquired.

The occurrence of the anomaly in siblings, reported here for the first time, lends support to the hypothesis that it is genetically determined even when appearing in adults.

Simple presumptive tests for the defect when suspected clinically are the demonstration of absence of isohemagglutinins and an unexpectedly slow erythrocyte sedimentation rate.

Although the defect appears to be permanent, its effects may in many instances be ameliorated by the administration of adequate amounts of gamma globulin and the appropriate use of antibiotics.

SUMMARIO IN INTERLINGUA

Agammaglobulinemia es hodie un ben establite e generalmente recognoscite entitate clinic. Illo ha essite observate le plus frequentemente in juvene pueros sed a vices illo occurre etiam in adultos de ambe sexos. Le characteristica principal de iste anomalia es que in illo le organismo del patiente es incapace a producer globulina gamma e anticorpores e deveni per consequente susceptibilissime a infectiones, ben que omne le altere fractiones proteinic del sero es normal.

Le presente reporto describe le casos de 7 tal patientes. Omnes esseva mascule. In 3, lymphadenopathia e splenomegalia esseva tractos prominente, e le diagnose de gigante lymphoma follicular, basate super le examine bioptic de nodos lymphatic, esseva o establite o considerate seriemente. Un de iste 3 patientes moriva. In su caso le examine necroptic monstrava nulle signo de lymphoma. Le altere 2 es ancora vivente, sed illes non exhibi ulle signo de progressive morbo lymphomatose. Del altere latere, ambes exhibi omne le symptomas de avantiate morbo hepatic resultante de hepatitis chronic.

Un quarte e quinte patiente habeva nulle globulina gamma del sero secundo un examine electrophoretic, sed illes possedeva isohemagglutininas e non esseva specialmente susceptibile a infectiones. Nulle signo de subjacente o concomitante morbos organic esseva detegibile. Tamen in un del 2 casos, le cellulas plasmatic del medulla sternal esseva marcatemente reducite. Il es possibile que iste phenomeno representa un leve grado del mesme defecto fundamental.

Le 2 ultime patientes del serie esseva fratres, ambes con longe historias de infectiones respiratori. Illes disveloppava chronic leucemia lymphocytic a un etate avantiate, e subsequentemente le examine electrophoretic de lor proteinas seral revelava que illes possedeva nulle globulina gamma. Iste phenomeno es rarissime in casos de leucemia. Il es probabile que illo occurre in iste combination per coincidentia e non como effecto del condition leucemic.

Le pathogenese de agammaglobulinemia es obscur. Altere autores ha stipulate duo differente mechanismos: un, de natura hereditari, causante le defecto in juveniles, e un altere, acquirite, causante lo in adultos.

Le occurrentia del anomalia in cognatos a patre e matre identic—hic reportate pro le prime vice—pare supportar le hypothese que le defecto es determinate geneticamente mesmo quando illo se manifesta in adultos.

Simple essayos presumptive pro le diagnose del defecto quando su presentia es clinicamente a suspicer es le demonstration del absentia de isohemagglutinina e de un inexpectatemente lente sedimentation erythrocytic.

Ben que le defecto pare esser permanente, su effectos es meliorabile in multe casos per le administration de adequate quantitates de globulina gamma in combination con un appropriate uso de antibioticos.

BIBLIOGRAPHY

1. Bruton, O. C.: Agammaglobulinemia, Pediatrics **9**: 722, 1952.
2. Bruton, O. C., Apt, L., Gitlin, D., and Janeway, C. A.: Absence of serum gamma globulin, Am. J. Dis. Child. **84**: 632, 1952.
3. Janeway, C. A., Apt, L., and Gitlin, D.: Agammaglobulinemia, Tr. A. Am. Physicians **66**: 200, 1953.
4. Good, R. A., and Varco, R. L.: Successful homograft of skin in a child with agammaglobulinemia, J. A. M. A. **157**: 713 (Feb. 26) 1955.
5. Hayles, A. B., Stickler, G. B., and McKenzie, B. F.: Decrease in serum gamma globulin (agammaglobulinemia): report of three cases, Pediatrics **14**: 449, 1954.
6. Keidan, S. E., McCarthy, K., and Haworth, J. C.: Fatal generalized vaccinia with failure of antibody production and absence of serum gamma globulin, Arch. Dis. Childhood **28**: 110, 1953.
7. Prasad, A. S., and Koza, D. W.: Agammaglobulinemia, Ann. Int. Med. **41**: 629, 1954.
8. Grant, G. H., and Wallace, W. D.: Agammaglobulinemia, Lancet **2**: 671 (Oct. 2) 1954.
9. Sanford, J. P., Favour, C. B., and Tribeman, M. S.: Absence of serum gamma globulins in an adult, New England J. Med. **250**: 1027 (June 17) 1954.
10. Stern, K. G., and Reiner, M.: Electrophoresis in medicine, Yale J. Biol. and Med. **19**: 67, 1947.
11. Arends, T., Coonrad, E. V., and Rundles, R. W.: Serum proteins in Hodgkin's disease and malignant lymphoma, Am. J. Med. **16**: 833, 1954.
12. Rundles, R. W., Coonrad, E. V., and Arends, T.: Serum proteins in leukemia, Am. J. Med. **16**: 842, 1954.
13. Petermann, M. L., Karnofsky, D. A., and Hogness, K. R.: Electrophoretic studies on the plasma proteins of patients with neoplastic disease. III. Lymphomas and leukemia, Cancer **1**: 109, 1948.
14. Brown, R. K., Read, J. T., Wiseman, B. K., and France, W. G.: The electrophoretic analysis of serum proteins of the blood dyscrasias, J. Lab. and Clin. Med. **33**: 1523, 1948.
15. Adams, W. S.: Personal communication.
16. Wintrobe, M.: Personal communication.
17. Adams, W. S., Alling, E. L., and Lawrence, J. S.: Multiple myeloma: its clinical and laboratory diagnosis with emphasis on electrophoretic abnormalities, Am. J. Med. **6**: 141, 1949.
18. Krebs, E. G.: Depression of gamma globulin in hypoproteinemia due to malnutrition, J. Lab. and Clin. Med. **31**: 85, 1946.

ANTIBIOTIC PRODUCTS OF A VERSATILE FUNGUS *

By Sir Howard Walter Florey, *Oxford, England*

It is a very great honor for me to be asked to give this talk this afternoon as the recipient of the James D. Bruce Memorial Award. I need hardly say how very much I appreciate it and how highly an acknowledgment such as the present one is valued by those who come from other countries than yours. For there is no question that at the present time we all look to your great country as the originator and developer of most of the ideas which are now animating the medical scene, and so an award to someone outside your country is doubly flattering.

In turning over how I might fittingly commemorate James D. Bruce and his desire to bring forward the achievements of preventive medicine, it naturally occurred to me to look through the lectures of your previous lecturers. Some have given a resumé of the work for which they were honored, and have tried to show how it had an influence on the improvement of human welfare. I felt it difficult to follow in their footsteps, for there are now almost innumerable original papers on the subject of antibiotics, and there are many excellent books, reviews, assessments, warnings, forecasts and descriptions of glimpses into the crystal ball, so that I felt I could really give you no pleasure or instruction today by trying to sketch in 25 minutes the influence of the use of antibiotics on the health of the public. Instead, I should like to tell you of some researches which have been pursued during the last few years on a very remarkable fungus.

In July, 1948, I received a letter from Dr. Blyth Brook who, during the war, had been Public Health Officer in Sardinia. Dr. Brook wanted to know if I would be interested in a fungus producing an antibiotic which had been isolated by Professor Brotzu at Cagliari. Brotzu had been looking for antibiotic-producing microörganisms in the sea near a place where there was an outflow of sewage, his idea being that possibly in this neighborhood organisms antagonistic to those in sewage might particularly be developed. Be that as it may, he isolated an organism in 1945, grew it on agar and showed that it produced an antibiotic active against a number of pathogenic bacteria. He published his work in 1948 in a journal containing contributions from the Institute of Hygiene of Cagliari, which does not appear in the World List. Two photographs accompanied this publication and from one of these a drawing has been made to secure better reproduction (figure 1).

Brotzu considered the organism to be *Cephalosporium acremonium*, and though the mycologists of the Baarn Collection in Holland were not pre-

* Presented as the James D. Bruce Memorial Lecture at the Thirty-sixth Annual Session of The American College of Physicians, Philadelphia, Pennsylvania, April 25, 1955.

pared to be so specific when subsequently asked to identify the fungus, it is certainly a Cephalosporium. He grew the fungus on a liquid medium, into which it secreted the antibiotic, which he endeavored to separate. Though he encountered many difficulties he made an active, though obviously impure, extract, which, together with culture fluid, was used for the parenteral treatment of patients suffering from typhoid fever and from infection with *Brucella melitensis*. The preparations were also used for local application. It was claimed that the patients benefited from his treatment, though his substance contained, as he pointed out, a pyrogen.

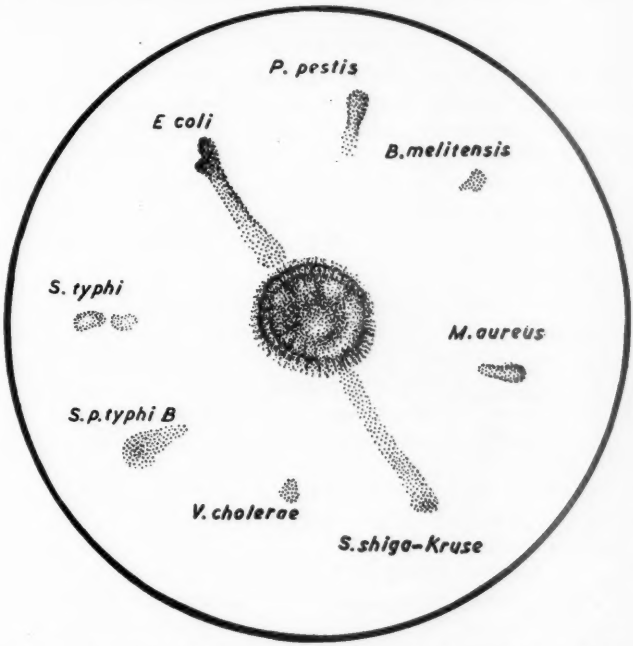


FIG. 1. Drawing (from illustration in article by G. Brotzu in Lavori dell'Istituto d'Igiene di Cagliari, 1948) showing the inhibition of a number of pathogenic organisms by his Cephalosporium.

A culture of the organism, received from Professor Brotzu in August, 1948, was cultivated by my colleague, Dr. Heatley, who was quickly able to confirm that it produced antibiotic material. The production of active culture fluid was further studied by Dr. Kathleen Crawford, and was later undertaken on a larger scale at the Antibiotics Research Station of the Medical Research Council by Mr. Kelly and his colleagues, who supplied concentrates of active material. Work by Drs. Burton, Newton and

Abraham has shown that the culture fluid may contain at least seven different acidic antibiotics, and has led to the isolation of four of them in a crystalline form.

The antibiotics produced by this fungus fall into two different groups. The members of one group are soluble in common organic solvents, whereas those of the other are not. The first group was named cephalosporin P, and was found to consist of a main component called P_1 and other similar but distinct components which were present in smaller quantities and were known as P_2, P_3, P_4 and P_5. The second group has been found to contain a new penicillin and a substance possibly related to penicillin.

Cephalosporin P_1

Chemical Investigations: This main component, together with other members of the P group, was extracted from the culture fluid into butyl acetate. After chromatography and counter-current distribution between solvents P_1 was obtained in crystalline form. Cephalosporin P_1 contains carbon, hydrogen and oxygen only (Burton and Abraham, 1951)[9] and it is possible that it has a steroid structure (Burton, Abraham and Cardwell, 1954, unpublished). So far as I am aware, no antibiotic has hitherto been shown to belong to this class of compound.

Biological Investigations (Ritchie, Smith and Florey,[10] 1951).

Cephalosporin P_1 was tested against a number of bacteria, among which staphylococci, both sensitive and insensitive to penicillin, diphtheria bacilli and tetanus bacilli were found to be very susceptible to its action. The growth of a number of strains of staphylococci was completely inhibited at the end of 24 hours by a concentration of between 1,280,000 and 2,560,000.

In contrast to this, *Streptococcus pneumoniae, Str. viridans* and *Str. pyogenes* had little sensitivity, growth being inhibited only at about a concentration of 1 in 10,000. *Br. abortus, Br. melitensis* and *Bacterium coli* were even less sensitive.

There was found to be a considerable effect of inoculum size, as tested with the staphylococcus, for a millionfold increase in the number of bacteria inoculated reduced to one sixteenth the titer for complete inhibition. In the presence of 50% or more of serum its activity was reduced to about half, and in vitro staphylococci were shown to acquire resistance quite readily. Nevertheless, when a small inoculum was used a culture was sterilized in 24 hours by a concentration of 1 in 200,000.

Pharmacologic Properties: The $L.D._{50}$ intravenously for mice weighing 20 gm. appears to be between 10 and 15 mg., and when 5 mg. were given by mouth every 12 hours for five and one-half days no abnormalities were produced.

By assay of the blood serum by the hole-plate method it was shown that cephalosporin P_1 was absorbed after subcutaneous injection and after oral administration.

It might be expected that a considerable portion of the cephalosporin P that disappears from the blood would appear in the urine, but after a subcutaneous dose of 2 mg. to a mouse only one two hundredth of the material injected appeared in the urine in five hours. An equally small proportion was secreted in the urine of decerebrate cats, and little was found in the bile.

What happens to the drug that remains behind in the body is not known, but its activity may be enzymatically destroyed.

Protection Experiments: Five milligrams of the drug given by mouth twice a day protected nearly all mice infected with about 100 times the $L.D._{50}$ of staphylococcus, but infections produced by larger inocula of the staphylococcus were less well dealt with. Under comparable conditions, Aureomycin and Terramycin were considerably more effective. The relative failure of cephalosporin P_1 to control infection in animals did not appear to be due to the development of resistance to the drug by the bacteria.

Thus, though the drug is not so effective as Aureomycin or Terramycin against experimental infections, it is clearly a substance which is on the verge of being a useful chemotherapeutic agent.

Cephalosporin N (Penicillin N)

During the extraction and investigation of cephalosporin P, another antibiotic with quite different chemical properties was discovered in the culture fluid. This was called cephalosporin N. Unlike cephalosporin P_1, the new substance could not be extracted by common organic solvents. It was somewhat surprising to find that cephalosporin N was rapidly destroyed by the enzyme penicillinase, because its solubility and antibacterial properties were quite different from those of any penicillin hitherto known.

Cephalosporin N was obtained in a highly purified form by a process involving chromatography and counter-current distribution (Abraham, Newton and Hale,[2] 1954). It was found that this product could be broken down to yield penicillamine (a sulfur-containing amino acid present in all penicillins) and a new amino acid known as D-α-aminoadipic acid. These and other findings made it clear that cephalosporin N was a new kind of penicillin (Newton and Abraham,[7] 1954).

You will notice in figure 2 that in neutral solution penicillin G contains one negative charge, but that cephalosporin N, which has α-aminoadipic acid incorporated into its side chain, has two negative charges and also a positive one. It is this conjunction of negative and positive charges which makes the substance so different in its properties from other penicillins.

Derivatives of cephalosporin N have been made by coupling a number of simple substances with the amino group of the side chain. These modifications of the molecule, which result in the loss of the positive charge, are accompanied by a striking change in the physical and antibacterial properties of the substance.

Biological Investigations (Heatley and Florey,[6] 1953).

Bacteriologic Properties: Many organisms are sensitive to the action of cephalosporin N, but the difference in chemical properties from that of other known penicillins is reflected in differences in its antibacterial range.

Cephalosporin N has less than one hundredth of the effect of penicillin G on gram-positive pathogens such as *Str. pyogenes* and *Staphylococcus aureus,* but it is as effective as penicillin G, or more so, against some gram-negative organisms such as *S. typhi.* Other gram-negative organisms, such as *H. pertussis* and *H. influenzae,* appear considerably less sensitive to cephalosporin N than to penicillin G. It is unfortunately just as easily destroyed by acid and by penicillinase as penicillin G.

Pharmacologic Properties: Experiments in mice show that it is readily absorbed from a subcutaneous injection, and somewhat more slowly from the intestine. It appears to be excreted almost as quickly as penicillin G by the kidney of the mouse. It may be even less toxic for mice than

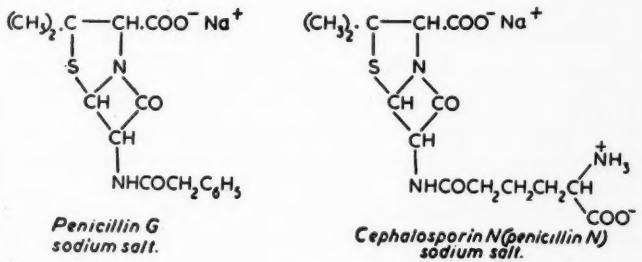


FIG. 2.

penicillin G, for the intravenous injection of 100 mg. of impure material causes little disturbance. This would be equivalent to 300 gm. injected intravenously in a man weighing 60 kg.

SYNNEMATIN B AND CEPHALOSPORIN N

While work on this substance was proceeding in Oxford a report appeared from the United States of a new antibiotic, synnematin (Gottshall, Roberts, Portwood and Jennings,[5] 1951). No suggestion was made that synnematin was a penicillin, but Abraham and his colleagues pointed out that the published data did not distinguish it from cephalosporin N (Abraham, Newton, Crawford, Burton and Hale,[1] 1953). Synnematin was later found to contain two antibiotics, synnematin A and synnematin B (Olson, Jennings and Junek,[9] 1953). After an exchange of material, cephalosporin N and synnematin B were compared, side by side, in Oxford and the United States, and it became almost certain that these two substances are identical and that they are both a form of penicillin, the chemical char-

acters of which have already been mentioned. It is now suggested that as the substance is a penicillin it might be called penicillin N, or aminocarboxybutylpenicillin.

Possible Clinical Uses: With its properties it is not surprising to hear that a number of cases of typhoid fever have been successfully treated with synnematin B. It is commonly assumed that penicillin is ineffective against the gram-negative bacilli, but with *S. typhi* in particular this ineffectiveness is only relative, and we did go so far some years ago as to suggest that penicillin might be used for the treatment of Salmonella infections (Florey and Jennings,[4] 1942).

We thus have to be careful in our assessment of the new penicillin before concluding that it will be more useful in treating typhoid fever than penicillin G.

FIG. 3. Skin reactions approximately half an hour after the intradermal injection of 0.1 ml. of—

arm on left—0.6 mg. cephalosporin N
arm on right—0.6 mg. (1,000 units) sodium penicillin.

This subject had been sensitized to penicillin by previous treatment.

It is possible that the new penicillin may have an advantage on occasion for patients who are sensitive to penicillin G, for it appears that they may not be affected by penicillin N. Garrod (unpublished) has tested the skin reactions of some patients and found in one that while there was a striking reaction to penicillin G there was none to penicillin N (figure 3).

CEPHALOSPORIN C

We have not yet exhausted a consideration of the products of Brotzu's mould, for during 1953 Newton and Abraham (1955) noticed that a sub-

stance which showed an absorption band at 260 mμ in ultraviolet light was present in crude penicillin N but was not present in more purified material. This substance, named cephalosporin C, they have now crystallized and found to be antibiotically active. Cephalosporin C, like penicillin N, contains nitrogen and sulfur and yields D-α-aminoadipic acid on hydrolysis, but unlike penicillin N it gives little, if any, penicillamine on hydrolysis. Nevertheless, there is evidence that the carbon skeleton of penicillamine is present in the molecule. At present, however, it is impossible to say what its exact relationship to penicillin is.

This substance is not inactivated at an acid pH nor by penicillinase from a strain of *B. subtilis,* but it seems that another enzyme, produced by *B. cereus,* can destroy its activity.

Biological Investigations.

Bacteriologic Properties: Cephalosporin C is active in vitro against a number of gram-positive and gram-negative organisms, but it is weak when compared with other antibiotics used in medicine (table 1). The growth of *Mycobacterium tuberculosis* is inhibited for some days at 200 μg./ml., but there is no inhibition at 16 days. The Shigellae are not affected. Strains of *Staph. aureus* which are insensitive to penicillin G because they produce penicillinase are as susceptible as those not producing it.

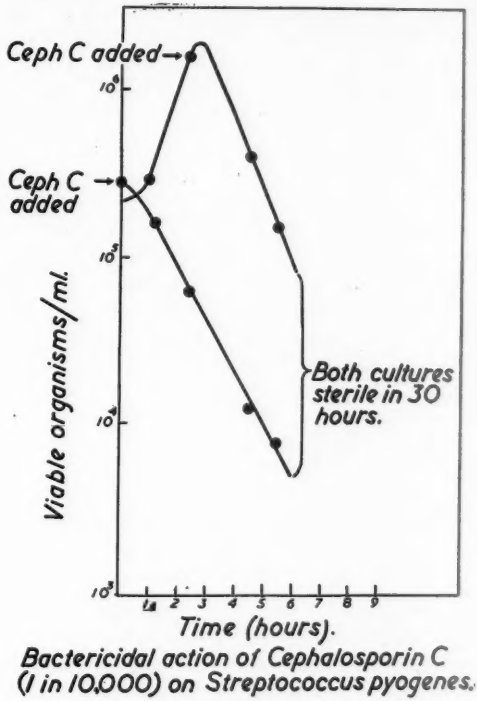
TABLE 1

Cephalosporin C

Organism		Lowest concentration inhibiting growth at 24 hrs., μg./ml.
Staph. aureus, Heatley strain Penicillin sensitive		50–100
Staph. aureus, Penicillin resistant		
8 strains of different phage types	1	25
	3	50
	4	100
31 strains not typed	2	12.5
	3	25
	16	50
	9	100
	1	400
Str. pyogenes		25
B. anthracis		25
N. meningitidis		1.6
N. gonorrhoeae		1.6
H. pertussis		1.6
H. influenzae		12.5
S. typhi		25
S. paratyphi B		25
S. typhimurium		50
V. cholerae		50
Bact. friedländeri		50
Bact. coli		200

It is bactericidal to such organisms as *Str. pyogenes* and *Staph. aureus* (figure 4).

Pharmacologic Properties: This substance, like penicillin N, is remarkably innocuous. Mice weighing 20 gm. given 10 mg., 50 mg. and 100 mg. intravenously showed no ill effects whatever from the injections. The substance is absorbed into the blood after subcutaneous injection and some is excreted in the urine. It is poorly absorbed from the gastrointestinal



Bactericidal action of Cephalosporin C (1 in 10,000) on Streptococcus pyogenes.

FIG. 4.

tract, though it is probably not destroyed there as it is not affected by an acid pH or by penicillinase.

Protection Experiments: The organism used was a strain of *Str. pyogenes,* virulent to mice. Though the L.D.$_{50}$ was not determined precisely, 0.5 ml. of a 1 in 1,000,000 dilution of culture repeatedly killed. In the experiments 0.5 ml. of a 1 in 10 dilution was used, and this killed all control mice within 12 hours. In vitro the growth of this organism was

completely stopped by a concentration of 25 μg. of cephalosporin C per milliliter.

In the first therapeutic experiment six mice that received eight doses of 2 mg. of the drug subcutaneously over a period of 24 hours, starting one hour after infection, were completely protected and remained well.

A second experiment was done to determine the smallest dose given in the same way that afforded complete protection. This proved to be 1 mg. given repeatedly. After the third dose of 2 or 1 mg., when control mice were very sick, the treated animals looked normal and the infection appeared to be already overcome. Eight doses of 0.5 mg. or 0.25 mg. prolonged life, but 0.125 mg. was without effect.

Two milligrams of cephalosporin C given every three hours by mouth had, however, no effect on a similar infection.

This substance thus has chemotherapeutic properties when used to treat artificial streptococcal infection in mice. Is it likely to have any uses in human medicine?

One of the problems of the present day is to treat what is apparently an increasing number of infections due to staphylococci which are resistant to penicillin G and other antibiotics. Cephalosporin C might well be an addition to the therapeutic means available for such treatment. Owing to its low antibacterial potency and the necessity to give large amounts, it would have what is probably a merit as far as new antibiotics are concerned—it would not be easy to give, for it is not readily absorbed when given by mouth. It might have to be given by continuous intravenous infusion, so that its use would be restricted to those seriously ill. The fact that it is not easily absorbed from the gut might well make it valuable in treating enteritis caused by staphylococci and other sensitive organisms.

Being bactericidal, it may have uses for local application to infections.

Conclusion

Thus the cephalosporium fished out of the sea by Brotzu has been found to produce an interesting variety of antibiotics. One of them, cephalosporin P, though inferior to several antibiotics commonly used in medicine, might conceivably be valuable in combating staphylococcal infection, although it has not yet been so tried in man.

A second is a new kind of penicillin, of which some physical, chemical and biologic properties are substantially different from those described for any other penicillin. It is conceivable that it may be useful for the treatment of typhoid fever and for use in patients sensitive to penicillin G. It offers possibilities for the manipulation of the penicillin molecule for the production of other antibiotically active substances.

And finally there has been isolated an antibiotic, cephalosporin C, which is possibly related in some ways to penicillin. It has, however, quite different physical and chemical properties and may have an application in

medicine especially for the treatment of staphylococcal infections resistant to other antibiotics.

You will now, I trust, agree with me that the title of this address, "Antibiotic products of a versatile fungus," was not inappropriate.

I am sure that you will envy me for having such skillful chemical colleagues who have unraveled the complexities of the antibiotics contained in the brew and have already made clear so much about their chemical properties and constitution. It is entirely due to their work that it has been possible to show some of the interesting biologic properties of the substances.

ACKNOWLEDGMENT

I am indebted to Dr. N. G. Heatley, Dr. M. A. Jennings and Dr. K. Crawford for permission to mention unpublished biologic work on cephalosporin C.

SUMMARIO IN INTERLINGUA

Viste que tante revistas e estimationes del effectos de antibioticos ha essite publicate, le presente contribution es facite pro signalar nove recercas in re un fungo que esseva discoperite per Professor Brotzu in Sardinia.

Il ha essite constatate que iste fungo produce al minus septe antibioticos acidic. Quatro de illos ha essite crystallisate (per Abraham, Newton, Burton, e Kelly *et al.*).

Un gruppo es solubile in commun solventes organic e contine substantias que ha essite nominate cephalosporina P_1, P_2, P_3, P_4, e P_5. On ha establite que cephalosporina P_1 es relativemente nontoxic e active contra staphylococcos resistente a penicillina. Illo pote proteger muses contra un parve inoculo de staphylococcos que suffice a occider omne controlos, sed illo es multo minus efficace que le tetracyclinas.

Le secunde gruppo es non-solubile in commun solventes organic. Le principal componente es le nove penicillina que contine acido D-alpha-aminoadipic. Illo ha perdite plus o minus completemente le capacitate de ager contra organismos gram-positive le qual es characteristic de penicillina G, sed illo es tanto efficace como penicillina G—e possibilemente mesmo plus efficace—contra *Salmonella typhi*. Il ha essite demonstrate que synnematina B es le mesme substantia. Es proponite pro illo le nomine penicillina N o amino-carboxybutyl.

Un altere antibiotico, possibilemente affin a penicillina sed non destruibile per acido o penicillinase, ha essite extrahite. Nulle effectos toxic esseva notate post le injection de 100 mg del substantia a in un mus de 20 g de peso. Plus alte doses non esseva administrate. Le activitate antibacterial del substantia es basse, sed illo es bactericidal.

Staphylococcos que es resistente a penicillina es afficite per le substantia, e il ha essite demonstrate que illo protege muses contra large doses de virulente streptococcos.

Es discutite le possibilitate del uso de iste substantias pro objectivos medical.

BIBLIOGRAPHY

1. Abraham, E. P., Newton, G. G. F., Crawford, K., Burton, H. S., and Hale, C. W.: Cephalosporin N: a new type of penicillin (Letter to the Editor), Nature, London **171**: 343, 1953.
2. Abraham, E. P., Newton, G. G. F., and Hale, C. W.: Purification and some properties of cephalosporin N, a new penicillin, Biochem. J. **58**: 94, 1954.
3. Burton, H. S., and Abraham, E. P.: Isolation of antibiotics from a species of Cephalosporium; cephalosporins P_1, P_2, P_3, P_4 and P_5, Biochem. J. **50**: 168, 1951.

4. Florey, H. W., and Jennings, M. A.: Some biological properties of highly purified penicillin, Brit. J. Exper. Path. **23**: 120, 1942.
5. Gottshall, R. Y., Roberts, J. M., Portwood, L. M., and Jennings, J. C.: Synnematin, an antibiotic produced by *Tilachlidium*, Proc. Soc. Exper. Biol. and Med. **76**: 307, 1951.
6. Heatley, N. G., and Florey, H. W.: A comparison of the biological properties of cephalosporin N and penicillin, Brit. J. Pharmacol. **8**: 252, 1953.
7. Newton, G. G. F., and Abraham, E. P.: Degradation, structure and some derivatives of cephalosporin N, Biochem. J. **58**: 103, 1954.
8. Newton, G. G. F., and Abraham, E. P.: Cephalosporin C, a new antibiotic containing sulphur and D-α-aminoadipic acid (Letter to the Editor), Nature, London **175**: 548, 1955.
9. Olson, B. H., Jennings, J. C., and Junek, A. J.: Separation of synnematin into components A and B by paper chromatography, Science **117**: 76, 1953.
10. Ritchie, A. C., Smith, N., and Florey, H. W.: Some biological properties of cephalosporin P_1, Brit. J. Pharmacol. **6**: 430, 1951.

INTESTINAL PARASITIC INFECTIONS IN FORSYTH COUNTY, NORTH CAROLINA. II. AMEBIASIS, A FAMILIAL DISEASE *

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SINCE Kofoid's [1] original report of an instance of familial infection by *Entamoeba histolytica* in 1923, evidence has gradually accumulated pointing to the family unit as an important element in the epidemiology of amebiasis. Shortly thereafter, a similar example of multiple infection in a family group was reported from Panama.[2] It was during the 1930's, however, that greatest attention was directed to prevalences within the domestic circle. In the course of a community study in Tennessee, 23 of 27 individuals comprising five families were found to be infected.[3] A study in Italy reported infection in seven members of a family of 10,[4] and in Guatemala, six of seven families resident in a rural community were found to have multiple infections.[5] Again in 1932, Kofoid called attention to the importance of the domestic unit in the epidemiology, stating: "Even under the best ordered sanitary discipline there is a tendency for the infection to spread in families." [6] The application of this was emphasized a year later by the report of three of four children infected by *E. histolytica* in a family of six resident in New York City. Since none of the children had been outside the sanitary area of the city, it appeared probable that the infection had been acquired within the domestic environment.[7]

The first extensive study of familial amebiasis was made in rural areas of Georgia.[8] Sixty-nine families comprising 290 persons were examined, and 55.9% were found to be infected. In several families the infection rate reached 90%, and in one, 10 of 11 members were infected. Subsequently, a report of the prevalence of amebiasis among children in New Orleans called attention to the fact that in almost every family concerned the infection could be demonstrated in at least one adult.[9] The significance of these observations was amplified by the finding that 71 of 76 mothers and 50 of 54 fathers were also infected by *E. histolytica.*[10] Further detailed studies threw addi-

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Studies conducted by the Department of Preventive Medicine and the Institute of Tropical Medicine of the Bowman Gray School of Medicine of Wake Forest College.
With the assistance of Mrs. Allen Holderman.

tional light on the role of the family unit in the transmission of this parasite. Statistical evaluation of the data collected demonstrated that the number of families having multiple infections among their members could not be the result of chance. Furthermore, there was a high degree of correlation between the size of the family and the prevalence of infection.[11] The maximal prevalence within the family was found among school children in the age group six to 16 years; adults in the household occupied an intermediate position; and the infection was least common among the pre-school children five years of age and younger.[12] Observations such as these give added force to Craig's dictum: "The finding of a single member of a family to be infected should be followed by the careful examination for this parasite of all remaining members of the family." [13]

Relatively few reports have been made of the prevalences of intestinal parasitic infections in North Carolina. In the period 1910–1914, the Rockefeller Sanitary Commission conducted extensive investigations of the distribution of hookworm infection in the Southern United States. The observed prevalence in North Carolina was 29.6%, and in Forsyth County it was 23.8%.[14] Since the completion of these initial studies the economic conditions and the standards of living and of sanitation have changed materially, particularly in the Piedmont region of the State. The passage of a statewide sanitary privy law, consolidation of rural schools with provision of adequate sanitary facilities, education of the public concerning the dangers of soil pollution and the establishment of full-time County Health Departments have materially reduced helminthic infections. In 1937 another survey showed that the prevalence of hookworm in the State as a whole had been reduced to 12.3% and in Forsyth County to 2.8%.[15] However, these studies devoted little or no attention to the intestinal protozoa.

During recent years interest in intestinal parasitic infections in the United States has been focused primarily on the protozoa, and particularly on the prevalence and epidemiology of *E. histolytica.* The paucity of information concerning the prevalences of these organisms in North Carolina, and the discrepancies encountered in the apparent prevalence of *E. histolytica* between the findings at the North Carolina Baptist Hospital in Winston-Salem and the rarity of the infection as shown by the records of the State Department of Health, demonstrated the need for factual data. Consequently a survey was initiated in 1950 and completed in 1952. The investigations were designed to provide competent data in four major fields: (1) the general prevalence of parasitic infections in a valid statistical sample of the population of Forsyth County; (2) the prevalence of amebiasis, and information concerning certain aspects of the epidemiology of the infection; (3) the usefulness of the examination of school children as a case-finding technic for the determination of the prevalence of *E. histolytica* in a community; and (4) evaluation of diiodo-hydroxyquinoline, U.S.P. (Diodoquin, NNR) for the mass therapy of amebiasis.

Epidemiology

The more authoritative estimates of the prevalence of *E. histolytica* in the United States vary between 5 and 10%[16] and approximately 20%.[17] Since man is both the predominant reservoir and the ultimate host, the local sanitary environment determines prevalence. In a discussion of the intestinal protozoa in 1913, Stiles[18] made an observation of fundamental importance: "Any given case of infection is prima facie evidence of fecal contamination of food and of insanitary surroundings. The indicator value of these protozoa (Entamoeba, Lamblia and Trichomonas), a thing which has been overlooked heretofore, is greater than that of *Bacillus coli*." More recently it has been pointed out by Connell and French[19] that "Amebic infection depends more on how one lives than where one lives."

Transmission of this infection has long been ascribed to polluted water supplies, the use of night soil as fertilizer for truck gardens, mechanical spread by flies, contamination of food by infected food handlers and the possible existence of naturally infected reservoir hosts other than man. However, until comparatively recently, *E. histolytica* has not been actually demonstrated except in association with man, flies and certain potential reservoir hosts.[20]

The characteristic endemicity of amebiasis provides circumstantial evidence that the use of polluted water is not a usual means of transmission of the infection. Comparison of the prevalences among families using polluted and unpolluted local water suplies has shown surprisingly little difference in the infection rate.[11] Although water undoubtedly plays a part in many regions where there is contamination of streams and shallow wells with human feces, the water-borne infections that have been investigated in detail are typically epidemic in nature and are characterized by a predominance of cases of clinical dysentery.

There is direct correlation, however, between observed prevalences, methods of excreta disposal and the general cleanliness of the domestic environment. Families using unsanitary privies have been shown to have higher infection rates than those having no toilet facilities. A similar correlation exists with respect to lack of cleanliness of the home.[11, 12]

The house fly has long been recognized as playing a significant role in the transmission of this infection. Its habits of feeding upon available feces and of regurgitation and evacuation at a subsequent feed permit contamination of food both by the contents of the intestinal tract and by material adherent to the feet and legs. Cysts of *E. histolytica,* viable on culture, have been recovered from the vomitus and from the droppings of flies up to 24 hours after an experimental feed upon infected material.[21, 22] Viable cysts have also been recovered from flies caught near latrines and in houses.[23]

The role of the infected food handler has long been a controversial subject. The most convincing evidence on the importance of the food handler's role has been presented by Schoenleber.[24] He found that after several years'

residence on Aruba, foreign personnel had an infection rate of 25% and that the rate among the food handlers was 33%. Improvements in hygiene, treatment of infected food handlers and refusal of employment to infected persons seeking positions as food handlers were followed within one year by a reduction of 50% and, after three years, by a reduction of 92% in the infection rate. Commenting on this report, Craig [13] remarked: ". . . these observations definitely prove the great importance of the food handler in the transmission of amoebiasis and . . . such a practical demonstration is worth far more than any laboratory experiment in proving that the food handlers must be controlled before we can hope to attain success in elimination of this infection."

Until recently, contact transfer of the infection directly or indirectly from contaminated objects other than food or drink has received little consideration. A study of the epidemiology in a New Orleans orphanage provided important findings concerning this possibility.[20] The infection had been heavily endemic in the institution for a period of many years. No explanation had been found, nor had it been possible to devise effective means of control. Examination of centrifuged washings and of NIH swabs taken from many areas in the institution demonstrated that cysts, morphologically corresponding to those of *E. histolytica*, could be recovered from the hands and the soiled underwear of the children, the bottom of the laundry chute, damp sand in the play box in the yard, the contents of the wading pool and the bottom of the wading pool after it had been drained. When these examinations were repeated two weeks after general sterilization of the entire premises with live steam, cysts of *Endolimax nana* and *Entamoeba coli* were found on a stairway used by all the children. These observations were interpreted to indicate that a period of approximately two weeks' time was required for environmental contamination to build up to a level detectable by direct examination. The conclusion was reached, therefore, that under certain conditions the respective epidemiologies of amebiasis and of oxyuriasis might be closely parallel. Another study of the epidemiology of amebiasis also yielded findings which seemed to be incompatible with transmission restricted to food handlers, flies and water.[11] Transmission by contact with infected persons seemed to fit the observed conditions best. An analogous investigation in another rural community led to similar conclusions.[12]

Statistical Planning

Forsyth County is situated in the Piedmont region in the central portion of the State of North Carolina. It has an area of approximately 409 square miles. According to the 1950 census the population totaled 146,135, divided by race and residence as follows:

Urban		Rural	
White	51,051	White	53,642
Negro	36,760	Negro	4,682
Total	87,811	Total	58,324

It was recognized that examination of stool specimens from a probability sample of the general population would be required to obtain an unbiased estimate of prevalences. However, the difficulties inherent in undertaking a general screening of the population precluded such a procedure. Therefore, the decision was made to determine the prevalence of parasitic infections among the school population rather than the general population. It was believed that for most of these infections the prevalence among school children would be somewhat higher than that among the general population. Additional bias, however, would be entailed since families without a child in school would not be represented in the study. This could be compensated for by statistical methods.

Preliminary calculations were made to determine the minimal sample size that would be adequate to show significant differences between the racial and urban-rural groups. A forecast of maximal expected rates of prevalence, viz., 15% was used in these calculations to assure an adequate number of school children. If the observed prevalences proved to be smaller than anticipated, the value of the data would be sufficient to permit proof of significance between groups with fairly small differences. The selection of 165 children in each category was deemed necessary to accomplish the objectives of the analytic survey. However, calculations showed that twice this number of children would be required to provide a sufficient number of infections by *E. histolytica* for the study of treatment methods. Finally, this minimal number was increased by 10% to compensate for anticipated refusals of coöperation and other problems in connection with the collection of stool specimens. This precaution proved extreme, since coöperation exceeded 90%. The final number of students examined, therefore, was slightly larger than that actually needed for the statistical purposes of the survey.

Grades II, III, IV and V of the school population were selected for examination. Grade I students were omitted because it was believed they were too young to provide optimal coöperation. Moreover, they were in school only for half-day periods. This limited period of time might require too large a dose of laxative to obtain the necessary fecal specimens. Furthermore, since the proposed survey was to extend over two school years, it would have been impossible to forecast accurately the number of students to be enrolled in each school during the succeeding year.

Grades VI and above were omitted since many students in this age group from poor socio-economic backgrounds may not go beyond Grade V; and it was believed that these older children would prove less coöperative.

The total school population in Forsyth County in 1950–1951 in the four grades selected for examination was 10,698. Of these, 2,063, or approximately one fifth of the total, were available in the six schools surveyed. A total of 1,934 was examined, a coöperation rate of 93.7%.

The individual schools in which the survey was to be conducted were chosen to give statistically valid samples of the white and Negro and urban

and rural populations in the middle and lower economic brackets. The sequence in which the six schools were studied was determined by chance.

Methods

Prior to the start of operations, a detailed campaign of instruction was conducted for the teaching staffs and the Parent-Teacher Associations of the individual schools.[25] In order to obtain maximal coöperation, as well as for the purposes of investigation, these groups were informed that all persons found to be infected by *E. histolytica* would be offered treatment without cost.[26]

Examinations in the schools were done room by room after a signed permission was obtained from the individual child's parents. On the day of examination, immediately on arrival at school in the morning, the children were given crackers and a phenolphthalein-chocolate laxative.* This preparation was chosen because of its familiarity to the people, its acceptability by children and adults alike, its effectiveness in producing specimens within the limited time available in the school day, and its complete freedom from toxicity and undesirable side-effects.

Immediately after collection of the individual specimens, direct examinations were made in the temporary field laboratory set up in the school building. These included saline and iodine smears and Quensel's-stained preparations, using the warm stage for motility studies and to hasten penetration of the stain. Thereafter the specimens were taken to the base laboratory for examination, using the zinc sulfate centrifugal concentration technic.[27]

The numerical methods by which the efficiency of a technic can be calculated are based upon examination of successive stool specimens. In the present study successive stool examinations were impractical, and observed prevalences and interpretations are based upon the examination of single specimens obtained by laxation. The calculated efficiency for the demonstration of *E. histolytica* by this technic was 59.0%. This was based upon the findings at the initial examination and the examination following placebo treatment.

Children found infected by *E. histolytica* and a limited number of children not found infected by this organism led to the "positive families" and to the "negative control families." The number of the latter was determined by statistical calculation to provide a comparable sample to determine the efficacy of the examination of school children as a case-finding technic within a community.[28]

For the purposes of the survey, a "family" was defined as including all persons living under the same roof and taking one meal together every day. The method of examination of these family members differed from that of the school children only in the greater time lag between evacuation and ex-

* This preparation was generously supplied by Ex-Lax, Inc.

amination of specimens. The person to be examined was requested to take the same laxative agent at night and to collect a stool specimen the following morning. These specimens were collected as promptly as possible and taken to the base laboratory for direct and concentrate examinations.

Findings

The examinations of the 1,934 school children revealed 118 infected by *E. histolytica*. No statistically significant differences were found between the white and Negro groups, or between the urban and rural groups irrespective of race. Infection was ubiquitous. The almost identical prevalence in three of the four groups of children was striking: 6.0% among the white urban, 6.9% among the Negro urban, and 6.3% among the rural Negro children. The lower prevalence of 4.9% among the rural white children was believed to stem from their much poorer coöperation, particularly in view of the fact that findings among their families showed higher prevalence rates than in any of the other three groups.

The infected children served as the probands or leads to the 94 positive families. These comprised a total of 449 persons, not including the children previously studied in the schools. Infections by *E. histolytica* were found in 102 of these individuals, a prevalence of 22.7%, a figure almost four times that found for the entire group of school children examined. The observed prevalences among the school children and the positive family members are shown in table 1.

The classification of rural or urban shown in table 1 refers to the location of the home and not the school which an individual child attended. Although there appear to be differences in prevalences between certain groups, when the data are arranged in accordance with the actual residence of the families, whether urban or rural, no statistically significant differences are

Table 1

Prevalence of *Entamoeba Histolytica* among School Children and Positive Family Members

Race and Residence	School Children			Positive Families		
	Number Examined	*Entamoeba histolytica*		Number Examined	*Entamoeba histolytica*	
		Number	Per cent		Number	Per cent
Grand Total	1,934	118	6.1	449	102	22.7
Rural White	408	20	4.9	67	18	27.0
Rural Negro	411	26	6.3	129	30	23.3
Urban White	562	34	6.0	116	20	17.2
Urban Negro	553	38	6.9	137	34	24.8
Total White	970	54	5.7	183	38	20.8
Total Negro	964	64	6.6	266	64	24.1
Total Urban	1,115	72	6.5	253	54	21.3
Total Rural	819	46	5.6	196	48	24.5

found. As was the case with the children, there was no significant racial difference in prevalence among the family groups.

The highest prevalence of *E. histolytica*, 27.0%, was found among the white rural families. The lowest prevalence, 17.2%, was observed among the urban white family members. Urban and rural Negro families fell into an intermediate position, with prevalences of 24.8 and 23.3%, respectively.

This distribution of *E. histolytica* differs from that found among the school children in that the lowest prevalence was found in the white rural children and the highest in the Negro urban children. This suggests that the higher percentage of refusals among the rural white children may have been largely responsible for the low infection rate found in that group.

Infections by *E. histolytica* were found in 211 of the 619 positive family members. This includes the children of these families who had been ex-

TABLE 2

Frequency of Multiple Infections by *Entamoeba Histolytica* in Positive Families, Including School Children (619 Individuals)

Race and Residence	Number of Families	Number Infections per Family										Total Infections	Average Number Infections per Family
		1	2	3	4	5	6	7	8	9	10		
Grand Total	94	38	29	8	11	5	2	–	–	–	1	211	2.24
Rural White	15	3	6	2	2	2	–	–	–	–	–	39	2.60
Rural Negro	20	8	5	2	1	3	–	–	–	–	1	53	2.65
Urban White	28	15	8	2	3	–	–	–	–	–	–	49	1.75
Urban Negro	31	12	10	2	5	–	2	–	–	–	–	70	2.26
Total White	43	18	14	4	5	2	–	–	–	–	–	88	2.05
Total Negro	51	20	15	4	6	3	2	–	–	–	1	123	2.41
Total Urban	59	27	18	4	8	–	2	–	–	–	–	119	2.02
Total Rural	35	11	11	4	3	5	–	–	–	–	1	92	2.63

amined in the survey of the schools. There was an average of 2.2 infected persons per family, and a prevalence in the group of 34.1%. The frequency of multiple infections is shown in table 2.

E. histolytica infections were demonstrated in more than one member of the family in 60% of the 94 families examined. In 31% two members were infected, and in one family 10 of the members were found infected.

Multiple infections within the domestic group were most common among the rural whites. Thus, 80% of the rural white families had multiple infections by *E. histolytica*. The urban and rural Negro families occupied an intermediate position, with approximately 60% of the families having multiple infections within the domestic group. The lowest incidence of multiple infections, 43%, was found among the urban white families.

The average number of infections per family was slightly greater among the Negroes than among the corresponding white family groups. This dif-

ference is not statistically significant and is attributable to the larger size of many Negro families.

The familial nature of amebiasis is dramatically demonstrated by tabulation of the percentage prevalence of *E. histolytica* within individual families, as shown in table 3.

In 27 of the 94 positive families examined, from 50 to 100% of the individual family members were found to be infected by *E. histolytica.* All the members of one white urban family were found to be infected.

The weighted average rate of infection per family among the 619 members of these 94 positive families was 34.1%. Stated in different terms,

TABLE 3

Percentage Prevalence of *Entamoeba Histolytica* in Positive Families, Including School Children (619 Individuals)

Per Cent Infected	Rural White	Rural Negro	Urban White	Urban Negro	Total Families
5–9	—	1	—	1	2
10–14	—	3	5	4	12
15–19	1	6	1	1	9
20–24	1	—	4	3	8
25–29	3	—	4	5	12
30–34	1	2	4	5	12
35–39	1	2	1	—	4
40–44	3	2	1	1	7
45–49	1	—	—	—	1
50–54	1	1	5	5	12
55–59	—	—	2	—	2
60–64	2	—	—	—	2
65–69	—	—	—	3	3
70–74	—	—	—	—	—
75–79	—	—	—	1	1
80–84	1	2	—	1	4
85–89	—	1	—	1	2
100	—	—	1	—	1
Total Families	15	20	28	31	94
*Weighted average per cent infected	$\frac{41}{91}=45.0$	$\frac{50}{169}=29.6$	$\frac{49}{165}=29.7$	$\frac{71}{194}=36.6$	$\frac{211}{619}=34.1$

* The weighted average per cent infected is an average of the individual percentages weighted by the size of the family upon which the percentage is based.

these findings indicate that if one member of a family is found infected by *E. histolytica,* there is a probability that one third of all members of his family would be shown, by the technics used in this study, to be infected. Since these technics gave only a 59% probability of demonstrating an infection, this corresponds to an actual familial infection rate of approximately 60%.

It will be noted from table 3 that there are no significant differences between percentages of infection among the rural Negro families and the urban Negro and white families. The highest prevalence of infection, 45.0%, was observed among the rural white families. This difference is statistically

significant and may be attributed to conditions of domestic sanitation. This phase of the survey will be discussed in a subsequent report.[29]

To evaluate the significance of the observed prevalence of 22.7% of *E. histolytica* among the 449 members of the positive family members of infected children requires comparison with the findings in a comparable control group. The design of the study to evaluate the potential usefulness of the examination of school children as leads to the prevalence of amebiasis provided the means for this. Two of the urban schools in Winston-Salem, one for white children and one for Negroes, were utilized for this aspect.

A group of 50 families of infected children attending these schools was examined. They are included in the total of the 94 positive families previously discussed. A similar group of 49 families of apparently uninfected children in Winston-Salem was utilized as controls. These two groups of families were statistically comparable in every respect except the presence of

TABLE 4

Prevalence of *Entamoeba Histolytica* among Positive and Negative Control Family Groups

Group	Individuals Examined	*Entamoeba histolytica*	
		Number	Per Cent
50 Positive Families			
Urban White	71	9	12.7
Urban Negro	137	34	24.8
Totals	208	43	20.7
49 Negative Families			
Urban White	53	0	0.0
Urban Negro	107	1	0.9
Totals	160	1	0.6

E. histolytica in the schoolchild. The examinations of the negative control families were conducted sequentially until the sample reached a magnitude sufficient to provide conclusive evidence of the significance of the observed difference. The findings are presented in table 4.

The figures for each group of families present the findings among the family members, exclusive of the children examined in the school survey. Among the 208 persons comprising the positive family members, infections by *E. histolytica* were found in 43, a prevalence of 20.7%. In contrast to this, among the 160 persons in the negative control group only one infection by *E. histolytica* was found, a prevalence of 0.6%.

In these two comparable groups, infections by *E. histolytica* were found to be about 30 times greater among the family members of infected children than among the family members of uninfected children. The details of this phase of the investigations are to be published subsequently.[28]

The racial distribution of infection in these two groups was strikingly different. Although the prevalence was almost identical among the children examined at the two schools (6.4% among the white children and 7.0% among the Negroes), infections by *E. histolytica* were found to be almost twice as numerous in the families of the infected Negro children as in the families of the infected white children.

There are two possible explanations for this statistically significant difference in Winston-Salem: that there was a lower standard of cleanliness and hygiene in the Negro families (this was not borne out by the observations of the homes by members of the survey team, although crowding was frequently noted); or that the external sanitary environment of the Negro families was significantly lower than that of the whites, and that it was accompanied by greater exposure to fecal contamination of food.

This observed distribution and prevalence of *E. histolytica* suggests that the sanitary environment of the urban Negro families was significantly below that of the whites in Winston-Salem, and that it was accompanied by conditions favoring the spread of infection. The studies of the sanitary environment in relation to the prevalence of amebiasis are to be reported subsequently.[29]

Conclusions

1. The observed prevalence of *E. histolytica* among 1,934 school children, Negro and white, constituting a valid statistical sample of the school population of Forsyth County was 6.1%.

2. In 94 families of infected children comprising 619 individuals, 211 infections by *E. histolytica* were found, an average of 2.2 cases of amebiasis per family, and a prevalence of infection of 34.1%.

3. When the children examined in the schools are excluded, the observed prevalence of *E. histolytica* in the remaining 449 members of the 94 families was 22.7%.

4. Sixty per cent of the families of infected school children had more than one infected person per family.

5. Infections by *E. histolytica* were found to be approximately thirty times more frequent among the family members of infected school children than among the family members of uninfected children.

6. Amebiasis is a familial disease, and multiple infections within the family are the rule rather than the exception.

7. The calculated efficiency of the diagnostic laboratory methods used throughout these studies for the demonstration of *E. histolytica* was 59%.

Summario in Interlingua

Previe studios per altere investigatores ha demonstrate le importantia del familia in le epidemiologia de amebiasis. Il esseva confirmate que le frequentia de multiple infectiones intra le familia non es accidental e que un correlation existe inter le grandor del familia e le numero del infectiones.

Proque le plus frequente occurrentia de *Entamoeba histolytica* intra le familia ha essite constatate inter infantes de etates ab 6 a 16 annos, il pareva plausibile supponer que le examine de scholares del annos II, III, IV, e V in le scholas elementari providerea evidentia del frequentia de amebiasis in le communitate.

Esseva examinate 1934 scholares urban e rural, blanc e negre, representante circa un quinto del scholares del annos mentionate in Forsyth County in Nord-Carolina. Ille individuos qui revelava un infection per *E. histolytica* in le curso del examines executate al scholas esseva usate como guidas a lor familias. Un simile gruppo de scholares pro qui le examine revelava nulle infection esseva usate como guidas al familias de controlo.

Le plano statistic del investigationes e le question del extension, composition, e selection del lots de population considerate esseva elaborate per le Departimento de Biostatistica del Schola de Sanitate Public al Universitate Nord-Carolina con le objectivo de assecurar un statisticamente valide interpretation del observate differentias de frequentia. Esseva calculate que le technicas usate in demonstrar le presentia de *E. histolytica* in le specimens individual del feces habeva un efficacia de 59 pro cento.

Le frequentia de *E. histolytica* observate inter 1934 scholares del annos II, III, IV, e V in scholas elementari esseva 6,1 pro cento. Le frequentia de infection inter 449 altere membros de 94 familias de scholares in qui infection habeva essite constatate amontava a 22,7 pro cento. Si le scholares mesme es includite in le numero total del membros del 94 familias, le gruppo se augmenta a 619 personas con 211 individuos inficite. Isto es un frequentia de 34,1 pro cento. Le numero median de individuos inficite esseva 2,2 per familia. In 27 del 94 familias de scholares inficite, le parasito se trovava in inter 50 e 100 pro cento del membros individual.

Un gruppo de 50 de iste familias esseva comparate con 49 simile familias de apparentemente non-inficite scholares in le mesme scholas urban. In le prime de iste duo gruppos le frequentia de *E. histolytica* esseva 20,7 pro cento; in le secunde, le gruppo de controlo, illo esseva 0,6 pro cento.

Le datos permitte le sequente conclusiones: (1) Amebiasis es un morbo familial, e multiple infectiones intra un familia es le regula plus tosto que le exception. (2) Infectiones per *E. histolytica* se trovava circa 30 vices plus frequentemente inter le membros del familias de inficite scholares que inter le membros del familias de scholares sin infection.

BIBLIOGRAPHY

1. Kofoid, C. A., quoted by Craig, C. F.: The etiology, diagnosis and treatment of amebiasis, 1944, The Williams & Wilkins Company, Baltimore.
2. James, W. M., and Decks, W. E.: The etiology, symptomatology and treatment of intestinal amoebiasis, Proceedings of the International Conference on Health Problems in Tropical America, 1924, United Fruit Co., Boston.
3. Meleney, H. E.: Community surveys for *Endamoeba histolytica* and other intestinal protozoa in Tennessee; first report, J. Parasitol. **16**: 146–153, 1930.
4. Dell'Aquila, T.: Sette portatori di *Entamoeba histolytica* su dieci componenti di una famiglia, Policlinico (sez. prat.) **37**: 981–983, 1930.
5. Mackie, T. T.: Iodoxyquinolin sulphonic acid (anayodin) in the treatment of intestinal amoebiasis, 1931, 20th Annual Report of the Medical Department, United Fruit Co., Boston.
6. Kofoid, C. A.: Amoeba and man, University of California Chronicle **34**: 149–170, 291–307, 1932.
7. Mackie, T. T., and Nauss, R. W.: Familial infection by *Endamoeba histolytica* in New York City, Am. J. Trop. Med. **13**: 577–582, 1933.
8. Seckinger, D. L.: The epidemiology of *Endamoeba histolytica* infection in two rural Georgia counties, South. M. J. **29**: 472–477 (May) 1936.

9. Loeber, M., and D'Antoni, J. S.: Some recent experiences with amebiasis in children, New Orleans M. and S. J. **100**: 276–278, 1947.
10. D'Antoni, J. S.: Concepts and misconceptions in amebiasis, Am. J. Trop. Med. and Hyg. **1**: 146–154, 1952.
11. Eyles, D. E., Jones, F. E., and Smith, C. S.: A study of *Endamoeba histolytica* and other intestinal protozoa in a rural West Tennessee community, Am. J. Trop. Med. and Hyg. **2**: 173–190, 1953.
12. Jones, F. E., Smith, C. S., and Eyles, D. E.: Epidemiological study of *Endamoeba histolytica* and other intestinal parasites in the New Hope community. A restudy after 21 years, Am. J. Trop. Med. and Hyg. **3**: 266–275, 1954.
13. Craig, C. F.: The etiology, diagnosis and treatment of amebiasis, 1944, The Williams & Wilkins Company, Baltimore.
14. The Rockefeller Sanitary Commission for the eradication of hookworm disease, Publication No. 9, Washington, D. C., 1915.
15. Keller, A. E., Leathers, W. S., and Knox, J. C.: The present status of hookworm infestation in North Carolina, Am. J. Hyg. **26**: 437–454 (Nov.) 1937.
16. Craig, C. F.: Amebiasis and amebic dysentery, 1934, Charles C. Thomas, Springfield, Illinois.
17. Faust, E. C.: The prevalence of amebiasis in the Western Hemisphere, Am. J. Trop. Med. **22**: 93–105, 1942.
18. Stiles, C. W.: Contamination of food supplies. The value of protozoa as an aid in determining fecal contamination of the food supply, Pub. Health Rep. **28**: 290–291, 1913.
19. Connell, F. H., and French, H. T.: The incidence and result of treatment of subclinical amebiasis, J. A. M. A. **113**: 649–653, 1939.
20. Ivanhoe, G. L.: Studies on the transmission of amebiasis in a children's home in New Orleans, Am. J. Trop. Med. **23**: 401–419, 1943.
21. Pipkin, A. C.: Filth flies as transmitters of *Endamoeba histolytica,* Proc. Soc. Exper. Biol. and Med. **49**: 46–48, 1942.
22. Sieyro, L.: Die Hausfliege (*Musca domestica*) als Ueberträger von *Entamoeba histolytica* und anderen Darmprotozoen, Deutsche tropmed. Ztschr. **46**: 361–372, 1942.
23. Harris, A. H., and Down, H. A.: Studies of the dissemination of cysts and ova of human intestinal parasites by flies in various localities on Guam, Am. J. Trop. Med. **26**: 789–800, 1946.
24. Schoenleber, A. W.: The food handler as a transmitter of amebiasis, Am. J. Trop. Med. **20**: 99–106, 1940.
25. Mackie, T. T. et al.: Intestinal parasitic infections in Forsyth County, North Carolina. VI. Methods for conducting a community survey of the prevalence of intestinal parasitic infections, in preparation.
26. Mackie, T. T. et al.: Intestinal parasitic infections in Forsyth County, North Carolina. I. Diodoquin for the mass treatment of amebiasis, South. M. J., in press.
27. Faust, E. C., D'Antoni, J. S., Adom, V., Miller, M. J., Peres, C., Sawitz, W., Thomen, L. F., Tobie, J., and Walker, J. H.: A critical study of clinical laboratory technics for the diagnosis of protozoan cysts and helminth eggs in feces, Am. J. Trop. Med. **18**: 169–183, 1938.
28. Mackie, T. T. et al.: Intestinal parasitic infections in Forsyth County, North Carolina. III. Amebiasis in school children; an index of prevalence in a community, Am. J. Trop. Med. and Hyg., in press.
29. Mackie, T. T. et al.: Intestinal parasitic infections in Forsyth County, North Carolina. IV. Domestic environmental sanitation and the prevalence of intestinal parasitic infections with special reference to *Entamoeba histolytica,* Am. J. Trop. Med. and Hyg., in press.

PREVENTION OF FIRST-ATTACK RHEUMATIC FEVER *

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TODAY we hear a great deal about the prevention of rheumatic fever. The leading slogan of the American Heart Association this year is, "Stop Rheumatic Fever." The campaign is accompanied by leaflets, illustrated brochures and films. Wide circulation has been given to a statement entitled "Prevention of Rheumatic Fever and Bacterial Endocarditis through Control of Streptococcal Infections."

The campaign is twofold: to prevent first-attack rheumatic fever in the general population, and to prevent recurrent episodes in individuals who have already had a first attack.

Prophylactic measures directed toward the second of these objectives have now become well established. Today there is little argument about the advisability of prophylactic administration of one of the sulfonamide or penicillin preparations for the individual who has recovered from a well established episode of rheumatic fever or rheumatic heart disease. Opinion may differ as to the choice of drug and the duration of therapy, but seldom as to the administration of some form of preventive treatment. Chemoprophylaxis or antibiotic prophylaxis is now generally looked upon as routine to protect a rheumatic individual against recurrent disease.

The prevention of first-attack rheumatic fever in the general population is a newer concept and is therefore the object of our present attention. The recommendations of the American Heart Association Committee on Prevention of Rheumatic Fever and Subacute Bacterial Endocarditis begin with the statement that 3% of untreated streptococcal infections in the general population are followed by rheumatic fever.[1] The argument then runs briefly as follows: Adequate and early penicillin treatment will eliminate streptococci from the throat and will prevent most attacks of rheumatic fever; therefore, when streptococcal infection occurs in any individual, penicillin treatment should be started immediately and effective blood levels maintained for at least 10 days.‡

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‡ The specific treatment schedule recommended by the American Heart Association is one of the following:

1. Benzathine Penicillin G: one intramuscular injection of 600,000 units for children; 600,000 to 900,000 units for adults.
2. Procaine penicillin with aluminum monostearate in oil: one intramuscular injection of 300,000 units every third day for three doses; double this dose for adults (600,000 units every third day for three days).
3. Oral penicillin: 250,000 units three times a day for a full 10 days. To prevent rheumatic fever by eradicating streptococci, therapy must be continued for the entire 10 days, even though the temperature returns to normal and the patient is asymptomatic.

We observe with interest—not unmixed with some concern—the recent and rapid development of community programs intended to put these recommendations into practice and to prevent first-attack rheumatic fever through control of streptococcal infections among school children. The essential feature of these programs is the culturing of the throats of children suspected of having streptococcal infections, and the early and adequate treatment of those whose throat cultures have been found to be positive for streptococcus. The objective is undeniably good, but the enthusiasm has grown at such a pace that there is danger that programs designed as experiments or demonstrations may acquire an aura of validity and reliability which is not yet wholly justified.

It behooves us, therefore, to look closely at the evidence and to study critically the applicability and effectiveness of recommended procedures.

Since, then, the frequency of rheumatic fever following untreated streptococcal infections—3% is the figure usually quoted—forms the origin and basis of efforts to prevent first-attack rheumatic fever, this is the first point which deserves study. The evidence comes from several sources: the incidence of rheumatic fever following epidemics of streptococcus infection which occurred before the introduction of sulfonamides or antibiotics; more recent epidemics which were not treated with these drugs for other reason; and from rheumatic fever following sporadic streptococcal infections which were carefully studied but not treated because they occurred in groups being used as controls in studies of the effectiveness of these drugs.

One of the early and classic epidemiologic studies is that reported by Thorwald Madsen from Denmark in 1926.[2] During the course of about a month in a small community, 840 cases of severe sore throat occurred in a milk-borne epidemic thought to be due to the hemolytic streptococcus. In 30 of these cases, rheumatic fever developed one to five weeks after the onset of sore throat, an attack rate of 3.6%. Other more recent epidemics of streptococcal infections have been followed by similar attack rates:

Location	Year	Streptococcus infection		Rheumatic Fever	
		Source	Number	Number	Per Cent
Denmark[2]	1926	Milk-borne	840	30	3.6
North Carolina[3]	1943	Food-borne	100	3	3.0
Boston[4]	1950	Scarlet fever	102	4	3.9
Wyoming[5]	1949–51	Tonsillitis	1,206	32	2.6

With the advent of effective antistreptococcal drugs the question naturally arose: Can these streptococcal infections be controlled, and can rheumatic fever be prevented in this large group of some three out of every 100 persons who develop streptococcal infections? Evidence has now accumulated to indicate beyond any reasonable doubt that, within

carefully controlled circumstances, this unfavorable sequence of events can be interrupted.

Rammelkamp and his associates, in their excellent epidemiologic studies at the Streptococcus Disease Laboratory at the Warren Air Force Base, have demonstrated that prompt and continued treatment of streptococcal infections of the throat may eliminate the streptococcus from the throat and may reduce by 96% the clinical manifestations of rheumatic fever which follow streptococcus infections.[5] In this Air Force Training Base, 798 individuals with streptococcal infections were treated with penicillin promptly and continually for a period of 10 days from the onset of the infection. In this study group only two developed definite evidence of rheumatic fever. A control group of 804 individuals with streptococcal infections was not treated with penicillin and in this group, 17 developed definite attacks of rheumatic fever.

These results have been obtained from a captive population in a military establishment. Can they be duplicated in the general population? Should a physician, whenever he sees a patient with an upper respiratory infection which may be due to streptococcus, immediately administer penicillin? The streptococcal infection itself may be relatively unimportant. But the risk of serious sequelae is high, and we have evidence that they can be prevented. If he starts therapy with a view to preventing these sequelae he does so with the knowledge that he must continue treatment for a minimum of seven to 10 days to achieve his purpose. More particularly, can children, the age group most vulnerable to rheumatic fever, be protected in a manner similar to that found to be effective in military groups? How far should we press preventive measures? Should penicillin be given to all children with respiratory infections, or only with those proved to be of streptococcal origin? These are very practical problems.

There have been those who maintain that any respiratory illnesses with a temperature of 101° F. or higher should be presumed to be hemolytic streptococcal infections and should therefore be treated with penicillin.[6] This is pressing preventive medicine too far.

A wiser course is to distinguish between those infections which are in fact due to the hemolytic streptococcus and those which are not. The former may be treated; therapy aimed at the prevention of rheumatic fever is not indicated for the latter. Acceptance of this principle has led to the development of the programs, referred to above, in which an attempt is made to discover and to treat streptococcal infections among school children, who, in a sense, constitute another captive population in their school groups.

The first of these programs was initiated in 1950 by the Youngstown Heart Association (Youngstown, Ohio), and has received wide attention. Bunn and Bennett have recently published a report of this program.[7] At the outset, in order to gain coöperation on a community-wide base, there was suitable discussion and publicity within the medical society and the

public at large. A small group of 100 grade school children was then chosen in order to establish methods and technics. A nurse, employed by the Heart Association, was stationed in the school every day; any child with a sore throat was sent to her. A throat culture was taken by the nurse and sent to a local laboratory for examination. Also, the nurse visited the home of any child who was absent because of sore throat or fever and took a throat culture in the home. If the throat culture was found to be positive for hemolytic streptococcus, the parents were notified and advised to call their family physician. At the same time the family physician was informed of the situation and his attention was called to the recommended treatment. The treatment which was recommended was 600,000 units of procaine penicillin in aluminum monostearate immediately on the first day of illness and repeated after a three-day interval.

In the second year of the study, the academic year 1952–53, three additional schools were included in the study, so that 1,017 children were then in the study. Of the 1,017 children, 650 had one or more cultures taken, and 52 children (8%) were found to be positive for hemolytic streptococci. Of these 52 children, only 15 received recommended treatment. During this time none of the children under observation developed evidence of rheumatic fever. Upon the basis of these initial results, the program has been expanded to include a different group of 12,000 school children.

A preliminary report of the Youngstown program was presented at the Annual Meeting of the American Heart Association in 1953. Following this report local heart associations undertook to develop similar programs. The Pennsylvania Heart Association and its chapters have been particularly active in this regard. Community programs, following the general pattern of the Youngstown program, have been initiated or are in the process of development in the Northwest Chapter, the Southwestern Chapter, Mercer County and Berks County.

The results of these more recently introduced programs are not yet published, but the data from Youngstown bring several questions to mind. In a group of 1,017 "normal" school children, there were 52 who had streptococcal respiratory infections confirmed bacteriologically. If one accepts 3% as the expected frequency of first-attack rheumatic fever following streptococcal infections, then it might have been expected that 1.5 of these children would have developed rheumatic fever if no treatment had been given. As Bunn points out, these figures are obviously too few to justify any conclusions having statistical significance. Now, however, with the study population increased to 12,000, it may be hoped that the results will help to answer important questions as to the value and practicality of these procedures.

It may also be noted that in the Youngstown program and in the similar programs being developed, adequate control groups are lacking. Valid

controls are difficult to establish. Of the children cultured and found to be positive, should alternate ones be treated? Can we in conscience withhold treatment which is so strongly recommended by the American Heart Association? Should alternate classes or comparable schools be used to establish control groups? Or can the children with positive cultures for whom treatment is recommended but who do not receive recommended treatment be used as controls? These are questions which vex the program planners; they must be met.

At the same time one should not overlook the values which cannot be expressed in quantitative and statistical terms. An integral part of these programs is an intensive effort to familiarize physicians, teachers and parents with the importance of early and adequate treatment of streptococcal infections. The Youngstown experience has already indicated that many children who would not have been treated previously now receive penicillin therapy because of the increased awareness of physicians and parents brought about by the constant reminder of its importance.

Let us now consider the position of the individual physician in private practice outside of the public school system and these local Heart Association-sponsored programs. To institute penicillin treatment for every child with a sore throat suspected of being streptococcal in origin, and to maintain effective penicillin blood levels for at least 10 days, calls for a considerable measure of therapeutic determination. Bacteriologic examination may not be practical or readily available, and the decision must be made on clinical grounds alone without recourse to the bacteriologic laboratory.

Fortunately a diagnosis can be made with confidence in many cases, owing to the characteristic nature of an acute upper respiratory infection due to the hemolytic streptococcus. Typically it begins suddenly with sore throat, headache and fever, which may rise as high as 103° or 104° F. Abdominal pain is not infrequent in children. Upon examination, when seen early in the course of the illness, the throat has a characteristic red, beefy appearance. A follicular exudate is usually present, but the absence of an exudate should not be considered as evidence against streptococcal origin. The regional lymph nodes at the angle of the jaw are generally swollen and tender. Suppurative otitis media and sinusitis, indicated by aural or nasal discharge, are frequent complications of streptococcal pharyngitis. When such signs and symptoms appear, a diagnosis of streptococcal infection may be made with confidence on the basis of the clinical findings. In such cases one hardly needs bacteriologic confirmation of streptococcal infection; penicillin may be administered immediately.

Not infrequently, upper respiratory infections are far less characteristic and yet still may be due to the hemolytic streptococcus. For these ill-defined infections, bacteriologic examination of the nasopharynx is necessary in order to arrive at a differential diagnosis.

Breese and Disney emphasize the difficulty of accurate diagnosis of

beta streptococcal infections on clinical grounds alone. When checked against bacteriologic cultures, the accuracy in both positive and negative cultures was about 75%.[8] Symptoms and signs may be suggestive of streptococcal infection, but throat cultures materially increased the accuracy of diagnosis.

Another point to be borne in mind in the use of penicillin is the possibility of reactions due to hypersensitivity to the drug. Urticaria, angioneurotic edema and joint pains, symptoms which are familiar after the administration of serum, may occur following penicillin. However, an accumulating body of evidence indicates that such reactions are relatively infrequent following either oral or intramuscular therapy. Large numbers of children and large numbers of persons in military establishments have been treated with oral or intramuscular penicillin. In these series, toxic reactions have not occurred with a frequency or severity sufficient to interfere with continuation of the procedure. Although penicillin is not a drug to be used carelessly or indiscriminately, available evidence indicates that severe or fatal reactions are quite rare and the usual reactions are far less to be feared than the possibility of rheumatic fever's developing in some three out of every 100 cases of untreated streptococcal infections.

Conclusion

We come then to the conclusion that, for the prevention and control of rheumatic fever, all respiratory infections should be given serious attention, particularly among children of school age, since this is the period when the incidence of first attacks of rheumatic fever is highest. For the present, until further experience has accumulated, it seems best to reserve judgment on the efficacy and practicality of programs involving mass culturing of the throats of school children. But in private practice, in the hands of a skillful physician, streptococcal infections can often be recognized clinically on the basis of characteristic symptoms and signs. For such patients, penicillin therapy may be started without waiting for bacteriologic confirmation. The less impressive respiratory infections which may also be due to the hemolytic streptococcus and which, if untreated, may also lead to rheumatic fever, are a more difficult problem. In such cases bacteriologic examination is of greatest value in order that penicillin therapy may be started promptly for those cases that are of streptococcal origin, while at the same time, unnecessary medication may be avoided for those patients who do not show evidence of streptococcal infection.

Summario in Interlingua

In nostre dies multo es dicite e multo es scribite super le problema del prevention de febre rheumatic. Le campania contra febre rheumatic ha duo objectivos: (1) Prevenir prime attaccos in le population general e (2) prevenir episodios recurrente in individuos qui ha jam habite lor prime attaccos.

Mesuras prophylactic concernite con le secunde de iste objectivos es ben establite. Chimoprophylaxis o prophylaxis a antibioticos es hodie considerate como routinari in proteger le patiente de febre rheumatic contra recurrentias del morbo.

Le prevention de prime attaccos de febre rheumatic es un plus recente concepto. Illo se basa super le observation que adequate e prompte tractamentos a penicillina pote eliminar streptococcos ab le gutture e que assi illos pote prevenir le majoritate del attaccos de febre rheumatic. De accordo con iste principio on ha instituite programmas communal que provide (1) le execution de culturas ab le guttures de omne juveniles suspecte de haber infectiones streptococcal e (2) le prompte e adequate tractamento de ille individuos in cuje casos le culturas revela le presentia de streptococcos. Al tempore presente e usque un plus grande fundo de experientias ha essite accumulate, il pare sage non judicar le practicabilitate de programmas que require le execution in massa de culturas ab le guttures de juveniles de etate scholar. Tamen, in le practica private il es frequentemente possibile recognoscer infectiones streptococcal clinicamente super le base de symptomas e signos characteristic. Quando tal casos exhibi un configuration typic, on pote comenciar le therapia a penicillina sin attender le confirmation bacteriologic. Plus difficile es le problema del minus impressionante infectiones respiratori proque etiam illos pote esser causate per le streptococco hemolytic e etiam illos—si non tractate—pote resultar in febre rheumatic. In tal casos le examine bacteriologic es de grandissime valor proque gratias a illo il deberea esser possibile initiar le tractamento a penicillina promptemente in omne casos de origine streptococcal e evitar un superflue medication in ille altere casos in que le infection non es causate per le streptococco hemolytic.

BIBLIOGRAPHY

1. Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections: a statement prepared by the Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis, appointed by the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association, Circulation **11**: 317–320 (Feb.) 1955.
2. Madsen, T., and Kalbak, K.: Rheumatic fever subsequent to some epidemics of septic sore throat, Acta path. et microbiol. Scandinav. **17**: 305 (3) 1940.
3. Commission on Acute Respiratory Diseases: A study of food-borne epidemic of tonsillitis and pharyngitis due to β-hemolytic streptococcus, type 5, Bull. Johns Hopkins Hosp. **77**: 143–210, 1945.
4. Weinstein, L., and Potsubay, S. F.: A comparison of "symptomatic treatment," gamma globulin, and penicillin in treatment of scarlet fever, J. Pediat. **37**: 291–306, 1950.
5. Rammelkamp, C. H., Wannamaker, L. W., and Denny, F. W.: The epidemiology and prevention of rheumatic fever, Bull. New York Acad. Med. **28**: 321–334 (May) 1952.
6. Massell, B. F.: Present status of penicillin prophylaxis of rheumatic fever, Mod. Concepts Cardiovas. Dis. **20**: 108 (Sept.) 1951.
7. Bunn, W. H., and Bennett, H. N.: Community control of rheumatic fever, J. A. M. A. **157**: 986–989 (Mar. 19) 1955.
8. Breese, B. B., and Disney, F. A.: The accuracy of diagnosis of beta streptococcal infections on clinical grounds, J. Pediat. **44**: 670–673 (June) 1954.

PREVENTION OF ACUTE NEPHRITIS *†

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BOTH acute rheumatic fever and acute glomerulonephritis are complications of group A streptococcal respiratory infections. Although significant advances have been made during the past decade in the prevention of attacks of rheumatic fever, little attention has been paid to the problem of preventive measures for acute nephritis. This is especially surprising since both diseases are caused by group A streptococci, and the therapy of both the renal and cardiac complications can be considered inadequate today. In the present report, the natural history of acute glomerulonephritis will be emphasized in an attempt to focus medical attention on those features of the disease which may be susceptible to vigorous preventive measures.

NATURAL HISTORY OF ACUTE NEPHRITIS

The patient with an initial attack of acute nephritis usually seeks medical attention because of gross hematuria, swelling of the face or extremities, severe headache, vomiting or convulsions. The history of a respiratory infection beginning one or two weeks before the onset of nephritis is characteristic. From a clinical standpoint, there is little remarkable in the streptococcal infection that precedes an attack of acute nephritis. The infection usually involves the tissues of the oropharynx and tonsils, and may or may not be associated with a scarlatiniform rash. In some instances a skin infection has been observed to be the precipitating factor, and has been considered important in the pathogenesis of nephritis. In such cases the data are insufficient to rule out a concomitant infection of the respiratory tract or to establish the infection of the skin as the important factor in the genesis of the renal complication. It seems possible that strains of group A streptococci which produce nephritis may also show an unusual avidity to infect skin. To test this hypothesis, hamsters were infected by subcutaneous inoculation with several serologic types of streptococci obtained from different patients. Most strains from patients with nephritis produced a severe spreading infection of the skin and subcutaneous tissues, whereas such infections were observed only occasionally following inoculation with strains from patients with respiratory infections.[1] Therefore, the ability to pro-

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duce severe infections of the skin was not strictly limited to group A streptococci isolated from patients with nephritis.

One of the puzzling features of acute glomerulonephritis is that the attack rate is variable following proved streptococcal infections. This is in distinct contrast to rheumatic fever, where the attack rate in the general population is approximately 3% in patients who receive no therapy or inadequate therapy for the streptococcal infection. The reason for the marked variation in the attack rate for nephritis is the fact that only certain strains of group A streptococci are capable of initiating the disease. Nephritis may be extremely uncommon in certain years when no nephritogenic types are circulating in the population; in other years there may be more cases of nephritis than of rheumatic fever, since the attack rate of the former complication may be 10% or more following infections with nephritogenic types. In this country the majority of such nephritogenic strains belong to Lancefield's type 12, but strains of type 4, 25 [2] and a new strain named Red Lake [3] may also produce this complication. Thus, the serologic identification of the infecting strain of streptococcus becomes an important laboratory procedure.

The course of a type 12 streptococcal infection which was followed by an attack of acute glomerulonephritis is illustrated in figure 1. In this patient the urine showed 1, 20, 12 and 22 red cells, respectively, on the first, second, third and fourth days of the streptococcal illness. Subsequent examinations were within normal range until the fifteenth day, when 80 red cells were enumerated. The patient then developed edema, gross hematuria and hypertension. Albumin and red cell casts were observed in numerous specimens. The patient was followed for 18 weeks before the Addis count of the urine returned to normal values.

The latent period between the onset of the respiratory infection and the onset of nephritis is short, averaging only 10 days. This is in contrast to the long latent period, averaging 18 days, observed in attacks of acute rheumatic fever. This difference in latent periods may indicate basic differences in the pathogenesis of the two diseases but, more importantly, a short latent period presents a difficult problem to the physician who wishes to prevent the renal complication. This is especially true if the damage to the glomerulus occurs early in the course of the streptococcal infection itself.

Careful examination of the urine during the first few days of the respiratory illness yields valuable information concerning renal complications. The physician can frequently select those patients who will develop an initial attack of acute glomerulonephritis following the respiratory illness because the urine usually contains abnormal numbers of red cells and small amounts of albumin.[4] As the fever subsides the urine becomes clear, only to become loaded with red cells a few days later. Thus, the patient who excretes abnormal numbers of red cells during the first few days of a respiratory infection should be observed carefully for the development of renal complications.

NEPHRITIS FOLLOWING A TYPE 12 STREPTOCOCCAL INFECTION TREATED WITH GAMMA GLOBULIN

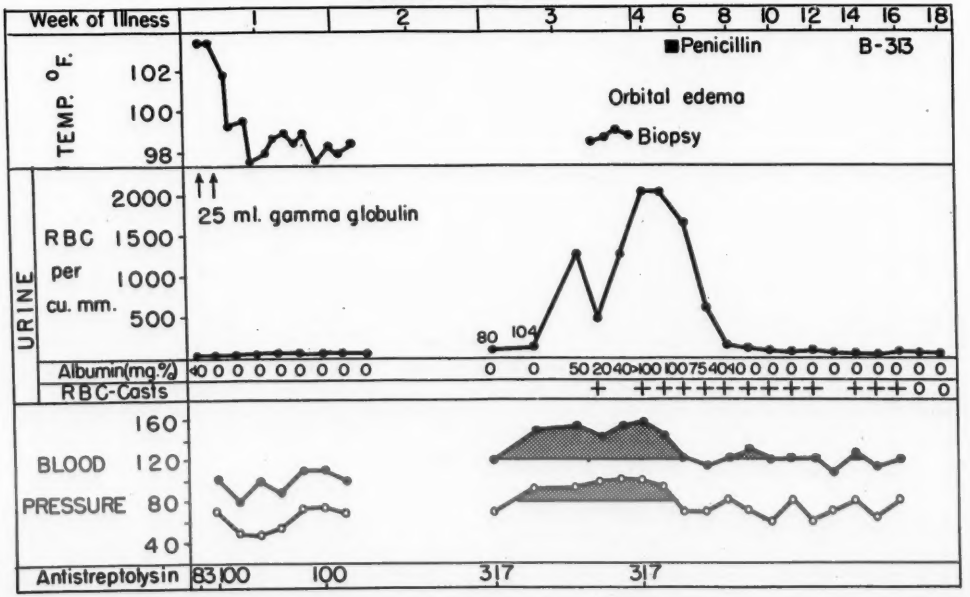

FIG. 1.

Patients who develop initial attacks of acute glomerulonephritis following a group A streptococcal infection usually recover, and there is little evidence to indicate that they subsequently develop chronic nephritis.[5, 6] It is true that many patients with nephritis gradually develop signs of increasing renal impairment,[7] but there is some evidence indicating that the nephritis in such patients was initiated by unrelated agents.[5] In any event, the physician's objective is to manage the patient with either acute or chronic renal disease in such a way that further impairment of kidney function will be prevented.

Prevention of Nephritis

The control of rheumatic fever is based on the fact that the disease is caused by an infection with group A streptococci. By the judicious use of antibiotics it is possible to control both initial and recurrent attacks of acute rheumatic fever. Theoretically, similar methods should be equally effective in the prevention of acute nephritis but, because of certain fundamental differences between the two complications, it is necessary to alter the preventive program.

Prevention of Initial Attacks of Nephritis: In the general population the only practical method presently available for the prevention of rheumatic fever is the treatment of the preceding streptococcal infection. To be effective, such therapy must eliminate the infecting organisms from the host. Chemotherapeutic agents administered in inadequate amounts fail to eradicate the streptococcus and do not alter the attack rate of acute rheumatic fever. The drug of choice appears to be benzathine penicillin, administered as a single injection of 600,000 to 900,000 units. Although early therapy of such infections is advisable, treatment instituted as late as the ninth day after the onset of the sore throat will still prevent rheumatic fever in the majority of patients.[8]

The problem of preventing initial attacks of acute nephritis in the general population appears somewhat more difficult than the prevention of rheumatic fever. Only one controlled study has been reported,[4] and the data are summarized in table 1. In this investigation of an epidemic of type 12

Table 1

Effect of Penicillin Therapy of Type 12 Streptococcal Infections on the Occurrence of Nephritis

Treatment	Number of Infections	Per Cent Developing	
		Nephritis	Hematuria*
Penicillin	44	4.5	6.8
Placebo	108	11.1	15.7

* Exclusive of nephritis.

streptococcal infections in a naval military establishment, acute nephritis developed in 11% of those patients who received no therapy. Another 16% showed abnormal numbers of red cells in the urine during the convalescent period but failed to develop other signs of nephritis. The administration of penicillin *early* in the course of the disease resulted in a decreased number of renal complications, but the results were not so dramatic as those obtained in studies designed to prevent rheumatic fever. Treatment with penicillin also decreased the number of patients who exhibited albuminuria during the convalescent period, but approximately 10% of the subjects who received therapy still showed some albumin three weeks after the onset of illness.

The failure to prevent renal damage in every patient receiving penicillin may be due to the short latent period exhibited by many patients developing nephritis. Thus, the glomerulus may be damaged early in the streptococcal disease, as evidenced by the hematuria occurring during the first few days of infection. Under such circumstances, perhaps a modification of the nephritic complication is the most one could expect from such treatment. In rheumatic fever, the evidence indicates that the rheumatic process is initiated late, usually after overt signs of the streptococcal infection have subsided.[8] From a practical standpoint, these observations emphasize the importance of *early* treatment of the streptococcal respiratory disease and indicate the need for the development of other preventive measures.

Following infection with most nephritogenic types of group A streptococci, the attack rate of acute nephritis is considerably higher than the attack rate of rheumatic fever. Furthermore, many inapparent examples of acute nephritis develop following infection with these organisms. For example, two siblings recently entered the hospital with symptoms of acute nephritis.[9] The disease first developed in a five year old boy who attended kindergarten in a small school. A survey of the children attending this school showed type 12 streptococci in the cultures obtained from many individuals attending kindergarten, but only a few were isolated from children in other classes. During the observation period of three months a total of 11 cases of nephritis was recognized among the children attending kindergarten or among their family contacts. Other children developed mild degrees of hematuria. No example of rheumatic fever was observed.

Epidemics such as that just described can be prevented. All individuals coming into intimate contact with the patient with nephritis should be cultured, and those shown to harbor *beta* hemolytic streptococci should receive an injection of 600,000 units of benzathine penicillin. By these measures the organism can be limited in its spread within the family and other population groups. Only by such methods can the incidence of nephritis be reduced appreciably. It would appear entirely reasonable to recommend that acute nephritis be made a reportable disease so that the public health authorities may assist in the development of effective control measures.

Prevention of Recurrent Attacks of Nephritis: It is now well established that patients who have had an attack of rheumatic fever are especially susceptible to recurrent attacks. From 20 to 80% of rheumatic patients experiencing a streptococcal infection will develop a new attack of rheumatic fever. It is for this reason that continuous prophylaxis is recommended for all individuals who have experienced an overt rheumatic episode.

The situation is somewhat different in the case of nephritis. Patients who have chronic nephritis frequently develop an acute exacerbation of the disease following a variety of infections. Characteristically, these episodes develop soon after the onset of the acute illness and no latent period is discernible. The urine specimens from these patients usually contain large amounts of albumin as well as numerous red cells and casts. In such patients the acute exacerbation may precipitate an episode of renal failure. It is therefore advisable to place all patients with signs of chronic nephritis on a prophylactic regimen. For this purpose oral penicillin may be administered in doses of 250,000 units once or twice daily or, as an alternative, a single intramuscular injection of 600,000 to 900,000 units of benzathine penicillin may be given at monthly intervals.

Patients who have developed acute glomerulonephritis following a streptococcal infection usually recover completely and fail to show an increased susceptibility to recurrent attacks. It seems possible that they may even be less susceptible to an attack of nephritis than the normal population. This statement is based on recent immunologic studies which indicate that the serum from patients who have had acute nephritis usually exhibits type-specific antibodies.[10] These antibodies persist for at least several years. Individuals with such antibódies have been shown to be resistant to infection by the homologous type of streptococcus, but normally susceptible to infection by other serologic types.[11] Since type 12 streptococci appear to be primarily responsible for most cases of nephritis in this country, the nephritic patient is already protected from infection with this organism. Since infection with most other serologic types will not precipitate a new attack in these patients, this group of patients does not require protection from streptococcal and other bacterial infections.

It should be emphasized that further knowledge of the immune status of the patient who has had acute nephritis is needed. This is especially true today, when the majority of patients with acute nephritis receive penicillin. Such therapy may inhibit type-specific antibody formation, even though it is usually administered 10 days after the onset of the streptococcal infection. It is possible that a few of these patients will develop a second infection due to one of the nephritogenic streptococci, and that second attacks of nephritis will be observed. To date, no such instance has been described.

In summary, by the intelligent use of penicillin in the therapy of streptococcal infections the incidence of nephritis should decrease. Of special

importance is the recognition of the public health aspects of nephritis, since the physician has the opportunity to limit the spread of nephritogenic organisms by the proper prophylactic procedures.

SUMMARIO IN INTERLINGUA

Es presentate un revista del historia natural de acute glomerulonephritis. Attention special es prestate a ille aspectos del morbo que rende lo attaccabile per vigorose mesuras de controlo. Tractamento a penicillina, usate contra le precedente infection streptococcal, reduce le frequentia de acute nephritis como illo reduce le frequentia de acute febre rheumatic. Proque infectiones con streptococcos nephritogenic es frequentemente sequite per complicationes renal, omne effortio possibile deberea esser facite pro determinar si streptococcos del typo 12 es portate per individuos qui ha essite in contacto con le patiente de nephritis. Omne individuos in qui le organismo es constatate deberea reciper penicillina pro prevenir su propagation.

Patientes qui ha recuperate ab un attacco de acute nephritis non require le continue uso del prophylaxis specific que es usual pro patientes de febre rheumatic. Sed le patiente de chronic nephritis require protection contra infectiones bacterial.

BIBLIOGRAPHY

1. Saxton, R.: Unpublished observations.
2. Rammelkamp, C. H., Jr., and Weaver, R. S.: Acute glomerulonephritis. The significance of the variation in the incidence of the disease, J. Clin. Investigation **32**: 345, 1953.
3. Updyke, E. L., Moore, M. S., and Conroy, E.: Provisional new type of group A streptococci associated with nephritis, Science **121**: 171, 1955.
4. Stetson, C. A., Rammelkamp, C. H., Jr., Krause, R. M., Kohen, R. J., and Perry, W. D.: Epidemic acute nephritis. Studies on etiology, natural history and prevention, to be published.
5. Aldrich, C. A.: Nephritis, *in* Brennemann's Practice of pediatrics, 1943, W. F. Prior Company, Hagerstown.
6. Hansborg, H.: Examinations about prognosis of scarlatinal nephritis, Acta med. Scandinav. **61**: 570, 1925.
7. Addis, T.: Glomerular nephritis, diagnosis and treatment, 1948, The Macmillan Company, New York.
8. Catanzaro, F. J., Stetson, C. A., Morris, A. J., Chamovitz, R., Rammelkamp, C. H., Jr., Stolzer, B. L., and Perry, W. D.: The role of the streptococcus in the pathogenesis of rheumatic fever, Am. J. Med. **17**: 749, 1954.
9. Siegel, A. C., Rammelkamp, C. H., Jr., and Griffeath, H. I.: Epidemic nephritis in a school population. The relation of hematuria to group A streptococci, Pediatrics **15**: 33, 1955.
10. Rammelkamp, C. H., Jr.: Glomerulonephritis, Proc. Inst. Med. Chicago **19**: 371, 1953.
11. Wannamaker, L. W., Denny, F. W., Perry, W. D., and Siegel, A. C.: Unpublished observations.

THE PREVENTION OF RESPIRATORY INFECTIONS WITHIN FAMILIES * †

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FOUR general principles provide the theoretic basis for the prevention and control of any infectious disease, namely: (1) to eradicate the causative agent, (2) to destroy the reservoir of infection, (3) to break the chain of transmission, and (4) to increase the resistance of the human host. These principles have varying degrees of application and of effectiveness. Eradication of the causative agent may theoretically be an ideal procedure, yet it is not generally feasible. At the present time the principle can be applied only to a limited extent, such as the use of a sulfonamide drug in a restricted population group for the control of meningococcal infections, or the use of penicillin for the control of group A streptococcal infections. The principle of destruction of the reservoir of infection is tenable only in the case of animal diseases. Even in such diseases, as, for example, bovine tuberculosis in this country, this procedure alone has never been completely effective. The principle of breaking the chain of transmission, or of otherwise preventing spread of infection, has been most effective with the waterborne diseases and with those spread by insect vectors. The principle of increasing the resistance of the human host is best exemplified by specific immunization, which may be either passive, as in the case of the use of convalescent serum or gamma globulin in measles, or active, as in the case of immunization against diphtheria.

Certain of the above principles can be applied to a community without direct regard for its population, such as water purification, sewage disposal, destruction or reduction of an animal reservoir, and control of mosquito breeding. Still others can be applied to man on a mass scale, such as the immunization against diphtheria or smallpox, or sulfonamide chemoprophylaxis for meningococcal infections in defined population groups. Still others are most particularly suited for individuals and their families, such as the prevention of group A streptococcal infections in a patient who has had an attack of rheumatic fever, and, under some circumstances, in the family of such a patient. This last area is the special province of the internist, the pediatrician and the practitioner of medicine. For this reason, and also because of increasing evidence that the family unit is an im-

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portant factor in the spread of infection, I would like to discuss first the occurrence of respiratory infections in families, and then consider the problem of prevention of such infections.

Occurrence of Respiratory Infections in Families

Respiratory diseases are generally defined as those involving primarily the respiratory tract or those for which the respiratory tract is the portal of entry or of discharge of the infectious agent. Such a definition encompasses a large number of diseases, whose causative agents may be bacteria, viruses (including many of the common communicable diseases of childhood), fungi, and one rickettsial infection—Q fever. Such a definition does not, however, indicate the relative frequency of occurrence of various types of respiratory disease, a factor of considerable importance in pointing out areas where research is needed as well as those where preventive and control measures might most effectively be applied.

Many surveys and other types of investigation have been carried out to determine the true occurrence and relative importance of respiratory and other infectious diseases in families, and to define the importance of the home as a place of spread. No attempt will be made here to review these studies. Rather, as an example, a brief summary will be presented of certain aspects of a detailed study of illnesses in a group of Cleveland families carried out during the past eight years by the staff of the Department of Preventive Medicine of Western Reserve University.[1-5]

The population under observation has been composed of some 70 families and approximately 325 persons, and does not represent a cross-section of an urban population. The families were selected on the basis of stability in the community and an interest in coöperating in the study. Economically they are in the middle and upper classes and, with few exceptions, they live in individual houses. The parents are young adults and all the families have children. The procedures employed to observe the families include periodic examinations, weekly visits by field workers, daily records of symptoms maintained by the mother, and visits by a member of the staff at times of illness in order to describe the illness clinically and epidemiologically and to obtain specimens as indicated for diagnosis or for etiologic study. No diagnostic or therapeutic advice is given to the families by the members of the staff, but the information obtained is transmitted to the family physician.

The incidence of illnesses in this population group during a six year period (from 1948 through 1953) is shown in table 1. The average number of illnesses per person per year was 10.1, of which 6.6 were respiratory infections and 1.7 were gastrointestinal infections. All other causes of illness, including the common communicable diseases, accounted for 1.8 illnesses per person-year. Thus two thirds of the illnesses were respiratory infections. The relatively high rate of occurrence of illness in the population

TABLE 1

Incidence of Illnesses in the Family Study during a 6 Year Period from 1948 through 1953

Type of Illness	Average Number of Illnesses Per Person-Year
Respiratory	6.6
Gastrointestinal	1.7
Other	1.8
Total	10.1

(Based on approximately 15,700 illnesses and 525,000 person-days of observation.)

is accounted for primarily by two factors: (1) more than half of the population is made up of children, and (2) the criteria for diagnosis of an illness were such as to include minor illnesses that would ordinarily not be brought to the attention of a physician.

A diagnostic classification of the illnesses occurring during the six years is shown in table 2. Almost 95% of the cases were considered to be "common respiratory diseases," a category made up principally of the common cold, but including also undifferentiated grippelike acute respiratory illnesses. The second largest category was that of streptococcal infections, accounting for 3% of the illnesses. The third category, nonbacterial pharyngitis, made up 1.6% of the illnesses. Included in this category are illnesses caused by Coxsackie viruses, such as herpangina, and by the type 3 adenoidal degeneration, or AD agent of Huebner and his co-workers.[6-8] The remainder included influenza, the atypical pneumonias and pneumococcal pneumonia, and together accounted for slightly more than 1% of the infections.

It is thus apparent that the common respiratory diseases, principally the common cold, are numerically the most important of all the respiratory infections. The behavior of this group of infections has therefore been subjected to a considerable amount of study. As is well known, the incidence of these illnesses is highest in the winter and lowest in the summer. Attack rates decrease with increasing age, and mothers have more illnesses than do fathers. The incidence is greatest in preschool children who have siblings attending school, and is progressively lower in school children, pre-

TABLE 2

Diagnostic Classification of the Respiratory Illnesses Occurring in the Family Study during a 6 Year Period from 1948 through 1953

Diagnosis	Per Cent
Common respiratory diseases	94.3
Streptococcal infections	3.0
Nonbacterial pharyngitis	1.6
Influenza	0.7
Atypical pneumonia	0.4
Pneumococcal pneumonia	<0.1

(Based on 10,136 cases.)

TABLE 3

The Relative Frequency with Which Various Family Members Introduce the Common Respiratory Diseases into Family Households

	Relative Number of Index Cases
Fathers	1.00
Mothers	1.22
Children:	
Preschool	2.01
School, 6+ years	2.06
School, <6 years	3.01

school children without school siblings, mothers, and fathers, in that order. This incidence is reflected by the frequency with which various members of a family group introduce new respiratory illnesses into a household (table 3). The father introduces a new infection into the family less frequently than any other member. Relative to the father, then, the mother introduces respiratory illness 1.2 times as often, preschool children and school children six years of age or over, twice as often, and school children less than six years of age, three times as often. After introduction, the resultant spread depends upon the status of the first, or index, case (table 4). If the first case is a child less than 5 years of age, other children in the household will acquire the infection more than half the time and parents approximately a third of the time. If the index case is a child older than five years, or a parent, the attack rate is approximately one-half as great. As might be expected, the total number of illnesses in a family increases as the size of the family increases. Intimacy of contact within the household also influences the attack rate in individual family members.

Thus the home is an important place for the spread of respiratory infections, and it seems probable that the manner of spread within the household is somehow related to intimate contact or association and is not dependent on mass contamination of the air or dust. It is not possible to quantitate accurately the risk of the "home" against the risk of the "community outside of the home," but the home risk apparently is greater. It would therefore appear that the prevention of the spread of infection within

TABLE 4

The Spread of Common Respiratory Disease in Families as Influenced by the Status of the First or Index Case

First Case	% of Time Others Become Ill		
	Children		Parents
	<5 yrs.	>5 yrs.	
Children: <5 years	58	56	35
>5 years	26	30	25
Parents	23	20	22

the home would have an appreciable effect on the occurrence of respiratory infections.

Prevention of Respiratory Disease in Families

To return to the matter of prevention and control, it is evident that the major respiratory disease problem is that of the common respiratory diseases of undetermined etiology, presumably caused by viruses. Streptococcal infections, nonbacterial pharyngitis and influenza are next most important in terms of relative frequency. It is for these diseases, then, that effective preventive measures would yield the greatest benefit. This listing, however, would be quite different were it not for the effectiveness of control methods that have been and are being employed for such diseases as smallpox, diphtheria, pertussis and tuberculosis. These procedures must be continued.

There are at the present time no procedures or drugs by which respiratory illnesses caused by viruses can be controlled through attempts to eradicate the causative agents. It is possible, however, to eradicate group A streptococci from both cases and carriers by the use of penicillin,[9-10] and to eliminate the meningococcus by the use of sulfonamide drugs.[11] Penicillin in therapeutic doses should therefore be used in the treatment of group A streptococcal infection in the home, not only to prevent the occurrence of complications such as rheumatic fever or acute glomerulonephritis, but also to eradicate the organism and reduce the possibility of spread to other members of the family. When a case of rheumatic fever or glomerulonephritis occurs in a household, cultures of the throat should be obtained from other members of the family and those having group A streptoccoci should be treated with penicillin. Other antibiotics may be employed if the individual person is sensitive to penicillin, but in general they are not so effective in eradicating the organism. Similarly, the occurrence of a case of meningococcal meningitis in a household is justification for the administration of 1 to 2 gm. of a sulfonamide drug per day for two days to the other members of the household.

Prevention of transmission of respiratory infections from one person to another would appear to be the most hopeful approach in view of the high degree of spread that occurs in households. The agents causing respiratory infections have been thought to spread primarily by the air-borne route, that is, through the air by droplets, droplet nuclei and dust.[12] On the basis of this concept, many attempts have been made to sterilize or purify the air by such means as the oiling of floors and blankets to control dust, the use of ultraviolet light, the production of aerosols from the glycols and other chemical substances, and by ventilation procedures designed to increase the turnover of air and thus reduce air contamination. For similar reasons, various isolation procedures and masks have been employed to reduce or minimize contamination of the air. In general, none of these procedures

has been sufficiently effective to justify its application, despite the fact that in a number of studies there has been a marked reduction in the number of bacteria that could be found in the air while the control procedures were operating. These results raise the question as to whether air-borne infection is the truly important method by which respiratory illnesses are spread. As already indicated, the data dealing with the spread of infection in families suggest that intimate contact and not contamination of the air is somehow involved in effective transmission. Certainly further information is needed.

The final method of prevention and control is that concerned with increasing the resistance of the host. For the common cold and other common respiratory diseases at least, many attempts have been made to accomplish this result in a nonspecific manner through diet, vitamins, physical conditioning, alkalis, the use of drugs such as the antihistamines, and even tonsillectomy. All of the controlled studies that have been carried out have failed to indicate that any of these measures are effective. Chemoprophylaxis with penicillin or sulfadiazine for streptococcal and meningococcal infections has sometimes been referred to as a means of increasing the resistance of the host to infection. Such is not the case, however, and there is no alteration in the resistance of the host that is not solely dependent upon the presence of the chemotherapeutic agent and its bacteriostatic or bactericidal effect. No chemoprophylactic drug has thus far been shown to prevent the occurrence of respiratory infections caused by viruses.

The resistance of the host can be increased specifically, however, for certain diseases by immunization. Passive immunization, using convalescent serum or gamma globulin, has been shown to be effective in the prevention or modification of measles and in the prevention of infectious hepatitis. The value of such passive immunization has not been established, or is questionable, for such diseases as rubella, varicella, mumps and poliomyelitis.

The use of active immunization for the prevention of a disease requires that the causative agent of that disease be available for administration. Until recently no etiologic agents had been isolated and cultivated in the laboratory from cases of the common cold and other common respiratory diseases. Within the last two years, however, Hilleman and Werner [13] have reported the isolation of a new virus from cases of acute respiratory disease (ARD) in military recruits, and this virus has been shown to be related etiologically to at least one form of this disease.[14] Huebner and his associates [6, 7] have isolated five other similar but immunologically distinct types of viruses from tonsils and adenoids, and have demonstrated that the type 3 virus is associated with cases of nonbacterial pharyngitis and conjunctivitis. While the relationship of these viruses to the various types of respiratory disease is far from clear, it seems entirely probable that active immunization against certain of the respiratory infections may be feasible in the near future. Bacterial vaccines, or "cold shots," are of no value in the prevention of the common cold, nor is a bacterial vaccine available for group

A streptococcal infections. Active immunization against influenza has been shown to be effective in a number of studies, provided new strains of influenza virus can be isolated as they occur and can be incorporated in the vaccine in advance of an outbreak. In view of the generally mild nature of influenza during the past two decades, however, there has been some difference of opinion regarding the use of influenza virus vaccine for mass immunization of our population. It seems most reasonable at the present time to employ this vaccine in a limited way, such as in patients with heart disease for whom respiratory infections of any kind hold an unusually great risk, or for critical population units such as hospital staffs and military organizations.

In conclusion, methods of prevention and control are available for only a limited number of respiratory diseases of primary importance in this country today. Their application, however, has been to a large extent responsible for the decline in incidence and fatality of a number of infectious and communicable diseases, and the potential has by no means been exhausted. Such well known procedures as vaccination and immunization against diphtheria must continue. Newer procedures, such as the use of penicillin and sulfadiazine in the prevention of streptococcal infections and recurrences of rheumatic fever, must be extended. No truly effective methods are available now for prevention of the great majority of respiratory diseases caused by viruses. Continuing studies on the new respiratory tract viruses, on the cultivation of the viruses of measles and of chickenpox,[15, 16] and on virucidal and virustatic chemical compounds,[17] however, hold out real hope for the future.

SUMMARIO IN INTERLINGUA

Il ha quatro principios general que establi le base theoric pro le prevention e le controlo de ulle morbo infectiose. Illos require (1) le eradication del agente causative, (2) le destruction del reservoir de infection, (3) le interruption del catena de transmission, e (4) le reinfortiamento del resistentia del hospite human. Iste principios ha varie grados de applicabilitate e de efficacia. Certes inter illos es applicabile a communitates o a alteremente definite massas de population; alteres es plus particularmente appropriate pro individuos e lor familias. Iste ultime area es le dominio special del internista, del pediatro e del practicante de medicina general. Le familia es apparentemente un importante loco de diffusion de multe morbos infectiose, como per exemplo le commun infectiones respiratori de origine presumitemente viral, infectiones streptococcal, pharyngitis non-bacterial, e influenza. Consequentemente il es importante applicar le disponibile mesuras preventive intra le gruppos familial.

Methodos de prevention e controlo existe al tempore presente pro solmente un restringite numero del morbos respiratori que es currentemente de importantia primari in iste pais. Sed le application de iste methodos es a un alte grado responsabile pro le recedente frequentia e mortalitate de un serie de infectiones e morbos communicabile, e lor potential es certemente non exhaurite. Le ben cognoscite technicas de vaccination e immunisation contra per exemplo diphtheria debe continuar. Plus recente technicas, como le uso de penicillina e sulfadiazina in le prevention de infectiones streptococcal e de recurrentias de febre rheumatic, debe esser extendite. Nulle vermente efficace methodos es hodie disponibile pro le prevention del grande majori-

tate del morbos respiratori que es causate per viruses. Sed on ha forte bases pro expectar importante resultatos ab le nunc progredente studios in re le recentemente discoperite viruses del vias respiratori, in re le viruses de rubeola e varicella, e in re virocidal e virostatic compositos chimic.

BIBLIOGRAPHY

1. Dingle, J. H., Badger, G. F., Feller, A. E., Hodges, R. G., Jordan, W. S., Jr., and Rammelkamp, C. H., Jr.: A study of illness in a group of Cleveland families. I. Plan of study and certain general observations, Am. J. Hyg. **58**: 16, 1953.
2. Badger, G. F., Dingle, J. H., Feller, A. E., Hodges, R. G., Jordan, W. S., Jr., and Rammelkamp, C. H., Jr.: A study of illness in a group of Cleveland families. II. Incidence of common respiratory diseases, Am. J. Hyg. **58**: 31, 1953.
3. Badger, G. F., Dingle, J. H., Feller, A. E., Hodges, R. G., Jordan, W. S., Jr., and Rammelkamp, C. H., Jr.: A study of illness in a group of Cleveland families. III. Introduction of respiratory infections into families, Am. J. Hyg. **58**: 41, 1953.
4. Badger, G. F., Dingle, J. H., Feller, A. E., Hodges, R. G., Jordan, W. S., Jr., and Rammelkamp, C. H., Jr.: A study of illness in a group of Cleveland families. IV. The spread of respiratory infections within the home, Am. J. Hyg. **58**: 174, 1953.
5. Badger, G. F., Dingle, J. H., Feller, A. E., Hodges, R. G., Jordan, W. S., Jr., and Rammelkamp, C. H., Jr.: A study of illness in a group of Cleveland families. V. Introductions and secondary attack rates as indices of exposure to common respiratory diseases in the community, Am. J. Hyg. **58**: 179, 1953.
6. Huebner, R. J., Rowe, W. P., Ward, T. G., Parrott, R. H., and Bell, J. A.: Adenoidal-pharyngeal-conjunctival agents: a newly recognized group of common viruses of the respiratory system, New England J. Med. **251**: 1077, 1954.
7. Bell, J. A., Rowe, W. P., Engler, J. I., Parrott, R. H., and Huebner, R. J.: Pharyngo-conjunctival fever: epidemiological studies of a recently recognized disease entity, J. A. M. A. **157**: 1083, 1955.
8. Ginsberg, H. S., Gold, E., Jordan, W. S., Jr., Katz, S., Badger, G. F., and Dingle, J. H.: Relation of the new respiratory agents to acute respiratory diseases, Am. J. Pub. Health **45**: 915, 1955.
9. Wannamaker, L. W., Rammelkamp, C. H., Jr., Denny, F. W., Brink, W. R., Houser, H. B., Hahn, E. O., and Dingle, J. H.: Prophylaxis of acute rheumatic fever by treatment of the preceding streptococcal infection with various amounts of depot penicillin, Am. J. Med. **10**: 673, 1951.
10. Wannamaker, L. W., Denny, F. W., Perry, W. D., Rammelkamp, C. H., Jr., Eckhardt, G. C., Houser, H. B., and Hahn, E. O.: The effect of penicillin prophylaxis on streptococcal disease rates and the carrier state, New England J. Med. **249**: 1, 1953.
11. Phair, J. J., and Schoenbach, E. B.: The dynamics of meningococcal infections and the effect of chemotherapy, Am. J. Hyg. **40**: 318, 1944.
12. Langmuir, A. D.: Air-borne infection, *in* Maxcy, K. F.: Preventive medicine and public health, 1952, Appleton-Century-Crofts, Inc., New York, p. 152.
13. Hilleman, M. R., and Werner, J. H.: Recovery of a new agent from patients with acute respiratory illness, Proc. Soc. Exper. Biol. and Med. **85**: 183, 1954.
14. Dingle, J. H., Ginsberg, H. S., Badger, G. F., Jordan, W. S., Jr., and Katz, S.: Evidence for the specific etiology of "acute respiratory disease (ARD)," Tr. A. Am. Physicians **67**: 149, 1954.
15. Enders, J. F., and Peebles, T. C.: Propagation in tissue cultures of cytopathogenic agents from patients with measles, Proc. Soc. Exper. Biol. and Med. **86**: 277, 1954.
16. Weller, T. H.: Serial propagation *in vitro* of agents producing inclusion bodies derived from varicella and herpes zoster, Proc. Soc. Exper. Biol. and Med. **83**: 340, 1953.
17. Horsfall, F. L., Jr.: Chemotherapy of respiratory viral diseases, Pediatrics **13**: 593, 1954.

THE CLINICAL EPIDEMIOLOGY OF POLIOMYELITIS * †

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IN this discussion of the clinical epidemiology of poliomyelitis, attention will be focused on the family epidemiology of the disease. This seems a reasonable approach, for it is the family unit with which the clinician is concerned: he is called to see a sick patient, it is true, but as with many other diseases, the circumstances under which the patient became sick are intimately connected with events involving other members of the family group.

This concept is well illustrated in figure 1, which is a family chart, outlining the experience of one family infected with poliomyelitis virus, which has been studied by a member of the Yale Poliomyelitis Study Unit.[1] The family consists of the father (a physician), the mother and eight children. Between August 5 and 17 all eight children exhibited evidences of infection; three, aged 10½, nine and four, had paralytic attacks, of these the four year old twin died of bulbar poliomyelitis. The varieties of host response are illustrated by the clinical forms in which the disease appeared in this family, including one child, aged nine, who had a typical diphasic course, with a clear cut minor illness, followed by a period of well being, and then the major illness, associated with central nervous system signs and paralysis. Two children (aged 10½ and four) had the major illness only, and two (aged seven and four) had only the "minor illness," or abortive form. Since no virus studies were carried out, none of the abortive cases can be considered proved, but the circumstances strongly suggest that poliomyelitis virus was responsible for illnesses in all eight of the children in this family, even though only three had clinically diagnosable forms of the disease.

Such family outbreaks emphasize several important features in the epidemiology of poliomyelitis. First of all, the high rate of infection among household members of a frank case suggests that there is something about the type of contact in a family which is conducive to spread of the infection. And second, we are reminded that a simple explanation of the spread by person-to-person contact alone is not entirely satisfactory, for as the above family illustrates so well, the whole family seems to be infected as a unit, at the same time. The pattern is entirely different from the familiar one seen with measles, in which secondary cases follow the primary case after a characteristic interval. The situation with poliomyelitis poses the question,

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Is this not perhaps in part a *place* infection, as well as a contact one? Or, is the incubation period so short that secondary infections have all occurred within two or three days after the virus is introduced into the family? As yet there is no definite answer on these points.

Many studies on infection rates among close associates of cases have been carried out in the past 20 years, using monkey inoculation for the testing of specimens. The results, which have been summarized recently by Brown et al.[2] indicate a much higher incidence of inapparent infection in family associates of cases than in outside contacts, or in those with no

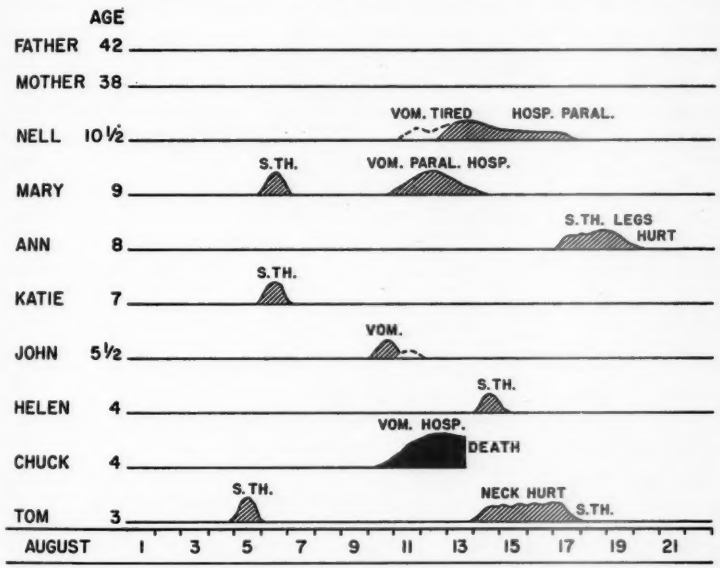

FIG. 1. A family outbreak of poliomyelitis (1) shown in the form of a schematic diagram. Shaded areas indicate periods of fever. S. Th.:—Sore Throat; Vom.:—Vomiting. A black area:—Death.

known exposure to a case. In the past few years it has been possible, with the introduction of tissue culture methods into poliomyelitis research, to extend the studies of the behavior of infection in families to include determinations of the serologic responses of those exposed. This correlation of virus excretion (or its absence) with immune status has yielded more accurate information on infection of susceptibles.[3, 4, 5]

By way of orientation in terms of the times at which one expects to find virus in various anatomic sites, figure 2 presents a schematic diagram in which the various forms or clinical manifestations are indicated: the biphasic course with a minor illness and a major illness, and the single phase, with a

major illness only; these two comprise the frank cases, either paralytic or nonparalytic, which are estimated to account for 1 to 2% of all infections. The abortive cases, in which only the minor illness occurs, are thought to represent 4 to 8%, while the majority of infections, 90 to 95%, are completely inapparent.

The evidence suggests that a few days after exposure, virus is present in the blood, throat and feces.[6, 7] This period may be accompanied by the minor illness, or it may be asymptomatic. In any event, virus soon disappears from the blood as antibodies appear, but it continues in the throat

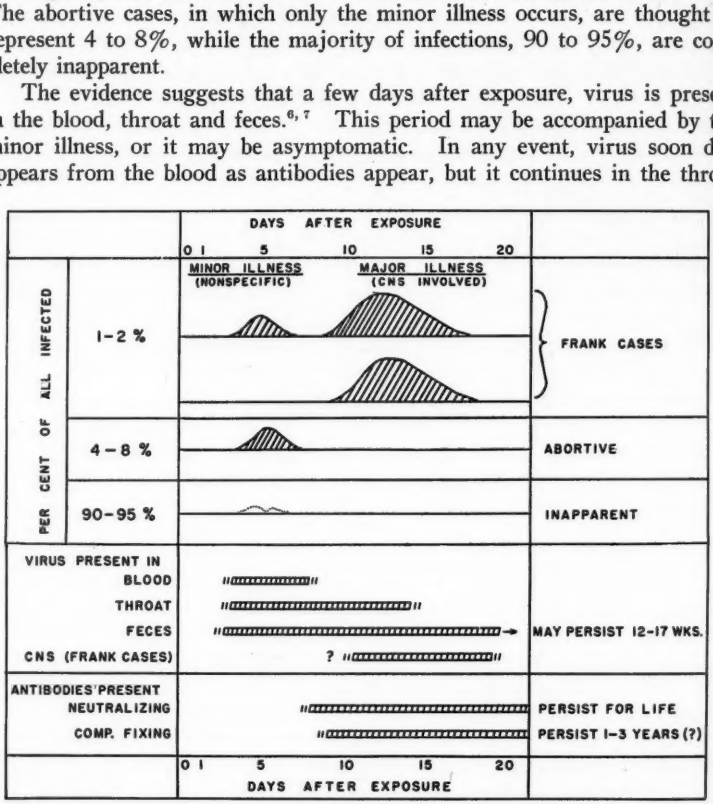

FIG. 2. Schematic diagram of the clinical and subclinical forms of poliomyelitis, correlated with the times at which virus is present in various sites, and the development of antibodies. (Redrawn from Paul, J. R.: The Epidemiology of Poliomyelitis, in W.H.O. Monograph Series, No. 26, Poliomyelitis, Geneva, 1955.)

for one to two weeks, or in the feces for as long as 12 to 17 weeks or more. Both neutralizing and complement fixing antibodies follow infection with poliomyelitis virus. The neutralizing antibody persists more or less for life, while the complement fixing one is transient, lasting probably nine months to several years or more.[8] A high titer of complement fixing antibodies is thus an indication of recent infection, and can therefore be of considerable diagnostic aid.

The way in which these laboratory tools—virus isolation and determination of antibody responses—can be utilized in studying the incidence

of poliomyelitis infection among susceptibles around a clinical case has been illustrated in several recent studies.[3, 4, 5] Table 1 summarizes some of the results of two of these. Brown, Rabson and Schieble [3] followed the excretion of virus and development of neutralizing antibodies in familial associates of cases after administration of gamma globulin (which had no demonstrable effect on virus excretion or the development of antibodies). Virus was isolated by these authors from 23 (or 42%) of the 55 persons whose stools were tested. In a comparable study of household contacts of cases carried out with Dr. McCollum in our laboratory, the remarkably similar result of 24 of 54 (44%) positive for the family type of virus was obtained. In both studies the highest incidence of infection was found in the younger age groups. This diminishing frequency of virus isolations with age has been observed many times before, and has been presumed to be due, in part at least, to an increasing number of immunes in the older age groups. That this is a likely explanation is indicated by the observation that when those individuals negative for virus were tested for the presence

TABLE 1

Infection Among Family Associates of Poliomyelitis Cases

Authors	Number of Contacts Studied	Virus Positive*		Virus Positive *or* Possessing Antibodies to Family Virus Type	
		Number	Per Cent	Number	Per Cent
Brown, Rabson and Schieble, U. Michigan study, 1953[3]	55	23	42	50	91
Horstmann and McCollum, Yale U. study, 1952[4]	54	24	44	49	91

* Virus isolated from throat or fecal material or both.

of neutralizing antibodies, 27 of 32 (84%) in the series of Brown et al., and 25 of 30 (83%) in ours, already had specific antibodies to the family type at the time the stool specimens were collected. Thus, in both of these studies 91% of familial associates of cases were *either* excreting virus *or* possessed specific antibodies.

More recently, the determination of complement fixing antibodies [8, 9] has added another means of defining more precisely the spread of infection through families. Since this antibody is a temporary one its presence in significant titer is an aid in designating recent infections. The following two families form a part of a recent, as yet unpublished study carried out in collaboration with Dr. Melnick and Dr. McCarroll.[5] The families were involved in a localized winter outbreak of poliomyelitis in January, 1955, in New York City; the epidemic seems to have centered around a nursery school, and the family contacts of the nursery school children. The "I" family (table 2) in which the first case occurred consisted of four members. The three year old girl, the first case in the outbreak, suffered a mild

TABLE 2

Poliomyelitis in the "I" Family

Name	Age	Diagnosis	Virus Isolation	Antibody Titers					
				Neutralizing* Type			Comp. Fixing* Type		
				I	II	III	I	II	III
Father	30	Well	Negative	64	64	0	0	0	0
Mother	29	Well	Negative	16	64	>1024	4	4	4
Patricia	3	Par. polio	Type I	256	0	0	>16	0	0
David	1½	"Minor illness"	Type I	256	0	0	>16	4	4

* Reciprocal of serum dilution.

paralytic attack. Type 1 virus was isolated from her rectal swab, and she developed both complement fixing and neutralizing antibodies to type 1. This was her first experience with poliomyelitis virus, since she had no neutralizing antibodies to either of the other two types. It was also the first experience of her brother, one and one-half years old, who had had a minor illness shortly before his sister developed her disease. Virus (type 1) was also isolated from this child, who developed a significant antibody response to type 1. As not infrequently happens, his serum showed a heterotypic complement fixing response to types 2 and 3 virus. Neither of the parents was infected, presumably because both had been infected previously, as demonstrated by the possession of type 1 neutralizing antibodies *without* significant complement fixing antibodies.

Another family (table 3) in the same outbreak illustrates what happens when virus is introduced into a home in which adults as well as children are susceptible, a not uncommon occurrence in 1955. The three year old boy in this family attended the nursery school. Type 1 virus was isolated from him and from his four year old brother; both had sharp type 1 antibody responses, with some heterotypic reaction as well. The one and one-

TABLE 3

Poliomyelitis in the "B" Family

Name	Age	Diagnosis	Virus Isolation	Antibody Titers					
				Neutralizing* Type			Comp. Fixing* Type		
				I	II	III	I	II	III
Father (case)	28	Par. polio.	Type I	64	0	0	>16	16	8
Mother	28	Well	Negative	256	0	0	0	0	8
Richard	4	Well	Type I	256	8	0	>16	0	8
Robert	3	Well	Type I	256	0	0	>16	8	16
Barbara	1½	Well	Negative	1024	0	0	16	4	16

* Reciprocal of serum dilution.

half year old sister was negative for virus but had a serologic pattern which indicates that she too had been recently infected with type 1. None of these children had been sick at any time recently. The father, on the other hand, developed paralytic poliomyelitis; type 1 virus was isolated from him, and his antibody response was also indicative of type 1 infection. Thus, as in the majority of infected families studied in this particular outbreak, one or both parents, and all of the children, were excreting virus or gave serologic evidence of infection.

The pattern of this small New York City epidemic, stemming apparently from an infected group of small children who introduced the virus into their families and infected their parents as well as their siblings, is not an unusual one. In the summer of 1954 a similar outbreak which occurred in New Canaan, Connecticut, was studied in our laboratory by Drs. Wilmer, Nolan and Melnick, who have kindly allowed me to quote their results.[10] In this instance, infection was introduced in some unknown manner into a nursery school consisting of 35 children. Of the children subsequently tested, 18 of 28 were found to be excreting type 1 virus. The children carried the infection into their homes, and in the course of several weeks a sharp epidemic occurred in which the majority of clinical cases were in adults. Studies of virus excretion and serologic responses, however, gave results similar to those in the family situations shown above.

The pattern of these two "nursery-school-borne" outbreaks emphasizes one of the striking features of the epidemiology of poliomyelitis: in the past 20 years there has been in the United States (and elsewhere) a marked shift in the age distribution of the disease, with a steady decrease in the percentage of cases occurring in young children, and a continually increasing percentage in young adults. In the two outbreaks described, virtually all susceptibles became infected, but *clinical attacks* of the disease were more frequent in adults than in children. This state of affairs might throw some light on the very puzzling problem as to why, when poliomyelitis virus attacks an entire family, some members develop severe paralytic—even fatal—disease, while others have only mild or completely inapparent infections. A number of possible explanations come to mind. The strain of virus involved is important: it is clear that some strains have a high paralytogenic capacity, while others have a low one. Virus dosage has also been shown experimentally to play a rôle: Sabin and Winsser [11] demonstrated that small amounts of virus fed to cynomolgus monkeys produce inapparent infection and immunity, while large amounts produce a high incidence of paralysis. Host factors, although less easily analyzed, have also long been presumed to play a dominant rôle,[12] and among these is age. When poliomyelitis is introduced into a community in which all age groups are fully susceptible, i.e., a so-called "virgin-soil" population, the age distribution of paralytic cases has a characteristic pattern, with highest attack rates in adults and marked sparing of young children.[13] Thus, there is evidence that with poliomyelitis, as with other virus infections such as hepatitis [14] and measles,[15]

susceptible adults, when exposed, are more apt to develop severe infections with a high mortality, while young children tend to experience mild or inapparent infections.[16]

This situation has particular significance for the internist in 1955, when poliomyelitis in the United States and certain other areas is less accurately than ever termed "infantile paralysis," when every year more and more cases are seen in young adults. As in some of the families which have been described, the physician is often called to see the father, or the mother, who is sick and who often presents rather a different and sometimes bizarre clinical picture as compared to the childhood pattern.[16] The patient, however, in this family disease, whether he has the paralytic or nonparalytic form, represents only a small part of the infections around him. In fact, one can assume that by the time a physician is called to see a case, virtually all other susceptible members of the family have been infected, whether or not they have symptoms.

Thus poliomyelitis has come to take its place among the most contagious of infections, alongside measles. In a family setting it spreads with speed and thoroughness to involve all susceptible members. It is thus a classic example of the importance of understanding the patient's illness in relation to his family and his home environment, if an accurate perspective is to be achieved.

Summario in Interlingua

In le presente discussion del epidemiologia clinic de poliomyelitis, nostre interesse es concentrate super le conducta del infection intra le familia. Durante multe annos le raritate de multiple casos de iste morbo intra un sol menage esseva un aspecto mystificante que le epidemiologo trovava difficile a explicar. Tamen, in le curso del passate 20 annos, plus e plus datos ha essite accumulate que indica que, ben que usualmente solo un caso recognoscite de poliomyelitis occurre intra le mesme familia, le altere membros e specialmente le juveniles monstra un alte frequentia del infection velate per le facto que illes non disveloppa ulle symptoma.

Per le uso del nove technicas de histocultura in le isolation de viruses e in tests serologic, on ha executate un serie de studios que indica que al momento quando un caso es recognoscite in un familia, practicamente omne le altere susceptibile membros del mesme menage es etiam inficite, lo que es manifeste per lor excretion de viruses e per lor disveloppamento de significative responsas anticorporal. Assi il appare que poliomyelitis—in contrasto con previe opiniones—es extrememente contagiose intra le ambiente familial, de facto tanto contagiose como per exemplo rubeola. Frequentemente un juvene portante de un non-apparente infection introduce le virus de poliomyelitis a in le menage e infice su fratres e sorores e non infrequentemente etiam su parentes. In un recente eruption localisate, que comenciava inter le infantes de un schola maternal, il esseva constatate que 15 familias esseva inficite. In 14 de iste familias, ultra le infantes etiam le patre o le matre o ambes esseva involvite, e 2 del 3 casos clinic occurreva in adultos. Il es evidente que iste situation ha un interesse special pro le medico contemporanee, proque in recente annos le frequentia del morbo inter adultos ha grandemente accrescite tanto in le Statos Unite como etiam in certe altere areas. E in reguardo a poliomyelitis—precisemente como in reguardo a altere morbos viral—adultos es plus susceptibile a prender le infection in un forma sever con un resultante augmentation del mortalitate.

BIBLIOGRAPHY

1. Horstmann, D. M., and Paul, J. R.: The incubation period in human poliomyelitis and its implications, J. A. M. A. **135**: 11–14, 1947.
2. Brown, G. C., Rabson, A. S., and Schieble, J. H.: The effect of gamma globulin on subclinical infection in familial associates of poliomyelitis cases. I. Quantitative estimation of fecal virus, J. Immunol. **73**: 54–61, 1954.
3. Brown, G. C., Rabson, A. S., and Schieble, J. H.: The effect of gamma globulin on subclinical infection in familial associates of poliomyelitis cases. II. Serological studies and virus isolations from pharyngeal secretions, J. Immunol. **74**: 71–80, 1955.
4. Horstmann, D. M., and McCollum, R. W.: Clinical and subclinical responses to poliomyelitis infection in families, J. Clin. Investigation **33**: 944, 1954.
5. Melnick, J. L., Horstmann, D. M., and McCarroll, J.: Unpublished observations.
6. Horstmann, D. M., McCollum, R. W., and Mascola, A. D.: Viremia in human poliomyelitis, J. Exper. Med. **29**: 355–369, 1954.
7. Bodian, D.: A reconsideration of the pathogenesis of poliomyelitis, Am. J. Hyg. **55**: 414–438, 1952.
8. Svedmyr, A., Enders, J. F., and Holloway, A.: Complement fixation with three types of poliomyelitis viruses propagated in tissue culture, Am. J. Hyg. **57**: 60–70, 1953.
9. Black, F. L., and Melnick, J. L.: The specificity of the complement fixation test in poliomyelitis, Yale J. Biol. and Med. **26**: 385–393, 1954.
10. Wilmer, B., Nolan, J., and Melnick, J. L.: Unpublished observations.
11. Sabin, A. B., and Winsser, J.: Immunogenic effect of repeated ingestion of minute amounts of poliomyelitis virus, Federation Proc. **12**: 456–457, 1953.
12. Aycock, W. L.: Study of the significance of geographic and seasonal variations in incidence of poliomyelitis, J. Prev. Med. **3**: 245–278, 1929.
13. Peart, A. F. W.: An outbreak of poliomyelitis in Canadian Eskimoes in wintertime, Canad. J. Pub. Health **40**: 405–417, 1949.
14. Capps, R. R., Bennett, A. M., and Stokes, J.: Endemic infectious hepatitis in a children's orphanage, Arch. Int. Med. **89**: 6–23, 1952.
15. Panum, P. L.: Observations made during the epidemic of measles on the Faroe Islands in the year 1846, 1940, Delta Omega Society, New York.
16. Horstmann, D. M.: Poliomyelitis: severity and type of disease in different age groups, *in* Proceedings of Conference on the Biology of Poliomyelitis, 1955, Ann. New York Academy of Sciences, in press.

THE CURRENT STATUS OF THE CONTROL OF INFLUENZA *

By THOMAS FRANCIS, JR., M.D., *Ann Arbor, Michigan*

IT has been my privilege on several occasions in the past 20 years to review before The American College of Physicians the status of knowledge of influenza. The studies of influenza, a disease of fearful history, represented, in many ways, the opening wedge in the dissection of that large body of common respiratory disease of probable viral etiology. The investigations have required the continuous close integration of clinical, epidemiologic and laboratory investigation to gain understanding of an extremely complex problem, and have contributed extensively to the philosophy and methodology necessary for further clarification of the entire field of respiratory disease. It is particularly opportune to reëxamine the state of progress at a time when the attention of the public and the medical world has been focused upon prevention of another virus disease by immunologic means.

The fact that influenza was not a simple disease immunologically was demonstrated by the studies of 1937–38 which disclosed the variation in strains of the virus that had first been identified in 1933–34 and was subsequently called Type A.[1, 2] In 1940, Type B virus was identified in our laboratory during a major epidemic prevalence;[3] in 1950, a virus recovered by Taylor [4] a year earlier was shown in our laboratory to be of epidemic character and was called Type C influenza virus.[5] More recently a virus isolated in Japan in 1952 [6] has been shown on serologic evidence to be prevalent in this country; on this basis and other characteristics we have suggested that it may be influenza D.[7] These represent major, distinct immunologic types without evidence of cross immunity. But the differences between strains of Type A and Type B also may be sufficiently sharp that cross immunity is not effectively obtained.

The best illustration of this fact occurred in 1947 when the strains we called A-prime appeared. It became apparent that immunity to the strains identified earlier did not protect against these mutants, although the latter could be readily shown to contain antigens also present in the earlier strains. This experience provided one other important observation: a change in antigenic composition of this extent, although the virus was widely epidemic, did not result in a highly fatal, pandemic disease. It seems highly probable that the factor of virulence is of great importance with respect to the severity

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Certain of these studies were conducted under the auspices of the Commission on Influenza, Armed Forces Epidemiological Board, and were supported by the Office of the Surgeon General, Department of the Army, Washington, D. C.

of the ensuing disease. The basis for the virulence of a strain is at present not clearly explained, but it is probably not merely a resultant of antigenic composition per se.

The complexity in this array of variation obviously presents problems in prevention of influenza by vaccination.[8] The fact that changes in composition of virus strains can be steadily expected has led to the suggestion that vaccination is not a practicable method of prevention. The counter proposal is [9] that the strains of virus belonging to Type A, for example,

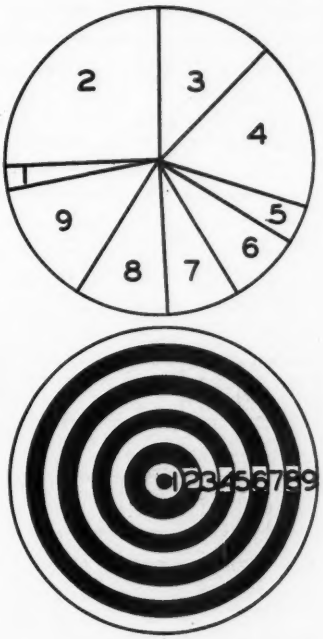

FIG. 1. Concepts of antigenic composition of influenza viruses.

possess a large number of antigenic components, varying primarily in quantity or in different degrees of prominence among the antigens (figures 1 and 2). On this basis, strains of virus containing significant quantities of the requisite components may be selected so as to provide adequate amounts of all the constituent antigens and thus furnish all the antigens of which that type of virus is composed. Recent studies even indicate that strains may be manipulated experimentally to alter the antigenic dominants, suggesting, thereby, that the necessary components for a complete vaccine can be arranged.

Moreover, studies of the distribution of antibody to different strains of virus have provided a further basis for understanding the immunologic needs of the general population. Some of the data which have led to a "doctrine of original antigenic sin" were presented to this assembly two years ago.[10] These investigations [11, 12] have pointed out the probability that the antibody which dominates the response of a person to influenza throughout his life is that which develops as a result of his first experience with virus of that type. Subsequent exposures broaden his antibody spectrum, but it is the primary response which subsequently becomes more and more dominant so as to characterize the person or the age group. Consequently, antibody to A-prime viruses is the most prominent in children; antibody to the characteristic A strains characterizes the group from

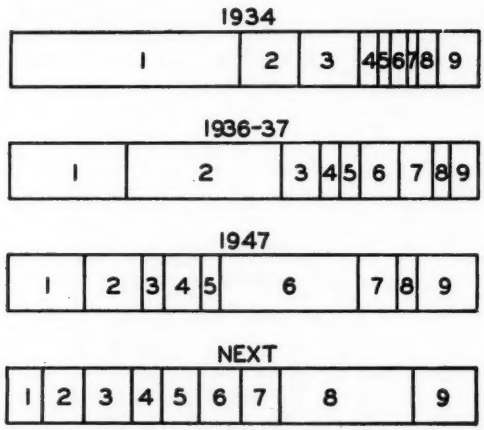

FIG. 2. Variation in strains of influenza virus.

15 to 30 years of age, while antibody to swine influenza is characteristic of those above 30 years of age. These differences recapitulate the chronologic periods of prevalence of the respective strains with surprising accuracy. They strongly support the concept that a strain of virus similar antigenically to swine influenza virus was the prevalent one in 1918—but also that it was not a completely new strain at that time, and it seems that it was exalted virulence which gave it its devastating qualities.

The results of these investigations demonstrate that the children are deficient in the A and swine antibodies, that young adults are deficient in swine antibodies, and that the older population is somewhat deficient in antibody to the A-prime strains. Since children are always the most susceptible members of the population and provide the highest incidence of influenza, it is reasonable to postulate that they are the ones who are most

in need of protection and in whom virus of different character would be most likely to gain epidemic headway. Hence, vaccination should seek to provide stimulus to antibody formation against antigens from strains which are not reflected in the naturally acquired antibody of that age group. This is a current objective.

It is not possible to review in detail the large number of studies which have been made evaluating the effectiveness of influenza vaccine. This has recently been done elsewhere (table 1).[13] But since 1943 the Commission on Influenza of the Armed Forces Epidemiological Board has conducted annual investigations in strictly controlled studies, with vaccines and placebo, which have consistently demonstrated that a properly constituted vaccine is highly effective (from 75% to over 95% effective) in prevention of influenza under epidemic or endemic conditions. Studies with adjuvants have indicated that the effect may be heightened and prolonged, but there are to date few data available as to the preventive effect. The low incidence

TABLE 1

Summary of Vaccine Experiments Conducted by Commission on Influenza

Year	Prevailing Type	Number Vaccinated	No. of Cases	Rate %	No. of Controls	No. of Cases	Rate %	Protection Ratio
1943	A	5,806	114	1.96	5,776	408	7.06	3.6
1945	B	1,150	10	0.87	2,150	241	11.21	12.9
1947	A-prime	10,328	743	7.19	7,615	616	8.09	1.1
1950	A-prime	670	8	1.2	2,082	78	3.7	3.1
1951	A-prime	2,596	13	0.5	5,228	105	2.01	4.0
1952	B	207	15	7.24	430	83	19.32	2.7
1953	A-prime	5,994	57	0.95	5,527	316	5.7	6.0 (corrected ratio = 8.1)
1953	A-prime	2,616	16	0.61	4,865	135	2.77	4.5

of the past few years has been a definite hindrance to that phase of the evaluation, but the results of the past winter, even though limited, support the evidence of improved antigenic response and the probability, therefore, of a firmer, more prolonged effect.

In summary then, the results of studies in vaccination with inactive influenza virus vaccine demonstrate its high effectiveness. Reactions are few, but persons naturally sensitive to eggs or chickens should not be given the vaccine. One can, in confidence, suggest that the broader use of the vaccine is desirable, and that it can sharply reduce the risk of influenza and other respiratory disorders which may accompany or follow it.

SUMMARIO IN INTERLINGUA

In recente annos le facto ha essite establite que ultra influenzas A e B etiam un typo C e un typo D es frequente. Iste ultimes ha usque nunc essite de importantia solmente limitate in eruptiones epidemic. Le varietate del stirpes intra le typos augmenta le complexitate del situation, sed on crede que le stirpes de cata typo

possede le mesme constituente antigenos e que lor differentias es determinate per differente dominantes. Iste conception permitte e reinfortia le spero que un vaccino pote esser elaborate in que omne le antigenos essential es representate. Information de alte valor ha essite colligite in re le distribution del anticorpores contra le differente stirpes in differente stadios de etate del population.

Es includite in le presente studio un résumé del nunc progredente studios controlate que es conducite per le Commission de Influenza. Le resultatos monstra uniformemente que un ben elaborate vaccino provide un alte grado de protection contra influenza, mesmo durante periodos de infrequente occurrentias del morbo. Il es a recommendar que vaccinationes contra influenza es usate plus generalmente.

BIBLIOGRAPHY

1. Magill, T. P., and Francis, T., Jr.: Antigenic differences in strains of epidemic influenza virus. I. Cross-neutralization tests in mice, Brit. J. Exper. Path. **19**: 273, 1938.
2. Francis, T., Jr., and Magill, T. P.: Antigenic differences in strains of epidemic influenza virus. I. Cross-immunization in mice, Brit. J. Exper. Path. **19**: 284, 1938.
3. Francis, T., Jr.: A new type of virus from epidemic influenza, Science **92**: 405, 1940.
4. Taylor, R. M.: Studies on survival of influenza virus between epidemics and antigenic variants of the virus, Am. J. Pub. Health **39**: 171, 1949.
5. Francis, T., Jr., Quilligan, J. J., Jr., and Minuse, E.: Identification of another epidemic respiratory disease, Science **112**: 495, 1950.
6. Kuroya, N., Ishida, M., and Shiratori, T.: Newborn virus pneumonitis (type Sendai). II. Report: The isolation of a new virus possessing hemagglutinin activity, Yokohama M. Bull. **4**: 217, 1953.
7. Jensen, K. E., Minuse, E., and Ackermann, W. W.: Serologic evidence of American experience with newborn pneumonitis virus (type Sendai), J. Immunol., in press.
8. Francis, T., Jr.: Significance of antigenic variation of influenza viruses in relation to vaccination in man, Federation Proc. **11**: 808, 1952.
9. Jensen, K. E., and Francis, T., Jr.: The antigenic composition of influenza virus measured by antibody-absorption, J. Exper. Med. **98**: 619, 1953.
10. Francis, T., Jr.: Influenza: the newe acquayantance, Ann. Int. Med. **39**: 203, 1953.
11. Davenport, F. M., Hennessy, A. V., and Francis, T., Jr.: Epidemiologic and immunologic significance of age distribution of antibody to antigenic variants of influenza virus, J. Exper. Med. **98**: 641, 1953.
12. (a) Davenport, F. M., Hennessy, A. V., and Francis, T., Jr.: Persistent antibody orientation resulting from primary experience with influenza viruses. I. Type of antibody response after vaccination, Federation Proc. **14**: 460, 1955.
    (b) Hennessy, A. V., Davenport, F. M., and Francis, T., Jr.: Persistent antibody orientation resulting from primary experience with influenza viruses. II. The antibody response following vaccination in individuals of varying experiences, Federation Proc. **14**: 465, 1955.
    (c) Jensen, K. E., Davenport, F. M., Hennessy, A. V., and Francis, T., Jr.: Persistent antibody orientation resulting from primary experience with influenza viruses. III. Characterization by serum absorption, Federation Proc. **14**: 466, 1955.
13. Francis, T., Jr.: Vaccination against influenza, Bull. World Health Organization **8**: 725, 1953.

THE MODERN MEDICAL TREATMENT OF PULMONARY TUBERCULOSIS *

By MAURICE J. SMALL, M.D., F.A.C.P., *East Orange, New Jersey*

IN a discussion of the modern medical treatment of tuberculosis it should be pointed out at the start that this treatment is still very young and that there are still many unanswered problems which are being actively investigated. Streptomycin (SM) did not come into general use until late 1947, para-aminosalicylic acid (PAS) in 1949, and iso-nicotinic acid hydrazide (INH) in 1952, and the concept of long-term chemotherapy with these drugs is quite new and its final evaluation far from complete. This discussion will therefore attempt to summarize what is currently accepted by the best authorities in the medical treatment of tuberculosis.

The cornerstone of modern medical treatment of tuberculosis is, of course, chemotherapy, and more particularly long-term chemotherapy. Medical collapse therapy has definitely been relegated to a minor rôle and will be referred to later. The tendency has been toward increased liberalization of the bed-rest regimen, and we shall say more of this later.

Several definitions are pertinent in our discussion, namely, the terms "active" and "inactive" tuberculosis, and "primary" and "reinfection type" tuberculosis. For purposes of this discussion an inactive lesion may be defined as one showing roentgen stability without evidence of cavity, and adequate negative bacteriologic studies for a period of at least six months. A lesion not filling these criteria is active. A primary lesion is the so-called first or childhood type of infection, and characteristically involves the lower portions of the lung field with a large, and often the major, component at the hilar lymph nodes. The reinfection type, or adult lesion, is the commonly seen upper lobe or infraclavicular infiltration, which tends to go on to cavity.

Granting that the advent of chemotherapy is responsible for the marked drop in tuberculosis mortality in the past decade from some 40 per 100,000 to roughly 12 per 100,000, and remembering, parenthetically, that the incidence of new cases annually is not showing a corresponding decrease by any means, the first question arises as to what type of lesion should be given chemotherapy. The general consensus is that all tuberculous lesions which are considered active should be given the benefit of chemotherapy. During the early years of chemotherapy it was felt by many that minimal active lesions should not be treated because the prognosis appeared to be so good

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without drugs. The specter of bacterial resistance seemed a terrible price to pay for a minimal lesion. Subsequent thinking, however, has changed in this regard. It is felt that a minimal infiltrate without presence of cavity is not a likely source for bacterial resistance, particularly when combined chemotherapy is utilized. Still undecided, however, and being investigated is the question of whether a primary tuberculous lesion should be given antimicrobial agents and, to carry the argument one step further, whether a person who has recently converted his tuberculin reaction from negative to positive should receive chemotherapy. The problem of the primary tuberculous lesion is assuming increased importance because it has been shown in recent years that the incidence of positive tuberculin reactors, even in a large urban population, has been rapidly decreasing.[1] This means that more and more adults as well as children are being discovered with primary types of lesions. This problem is currently being investigated in children in a controlled study by Dr. Edith Lincoln at Bellevue Hospital, and current thinking can be summarized as follows.

The utilization of chemotherapy for the primary type of pulmonary tuberculous lesion does not in any way accelerate its healing. Dr. Lincoln has noted this at Bellevue, and we have seen it repeatedly on the Pediatric Wards at Sea View Hospital. However, thus far no case of primary tuberculosis which has been treated with INH has as yet developed the complication of tuberculous meningitis, a complication which in the pre-chemotherapy era occurred not too infrequently and which has also occurred after SM-PAS treatment of the primary infection. The question is therefore being studied as to whether all primary tuberculous pulmonary lesions should not be given the benefit of a prolonged course of chemotherapy in a prophylactic manner, namely, for the prevention of tuberculous meningitis, disseminated hematogenous or miliary tuberculosis, and perhaps even reinfection-type tuberculosis at a later date. The logical extension of pushing the boundaries of chemotherapy back to include a fresh minimal lesion, and now primary lesions, leads to a consideration of the recent tuberculin conversion. Dr. James Waring, certainly an able and very experienced pthisiologist and internist, has recently presented a very cogent case for treating all those whose tuberculin reaction is known to have recently become positive.[2] This question is being actively debated and discussed at this time, and a final answer cannot be given.

Assuming, then, that all pulmonary tuberculous lesions considered active will be subjected to chemotherapy, and probably most primary lesions, the next question arises as to the optimal regimen of antimicrobial agents to be utilized. In general, the evidence is fairly conclusive that treatment should always be with at least two drugs, the reason being not so much the synergistic action between the two [3,4] but a rather convincing demonstration in large statistical series that the utilization of two drugs has made the emergence of resistant bacilli a relatively unimportant problem, except in

cases presenting large, thick-walled cavities which persist. Which two drugs, then, should one utilize? Are certain combinations more powerful than others as regards roentgen clearing and conversion of sputum? The answer, on the basis of a rather large amount of evidence collected by the Coöperative Chemotherapy Study of the Army, Navy and Veterans Administration, indicates that there is no difference in therapeutic efficacy of SM-PAS, SM-INH or INH-PAS. The question therefore resolves itself into utilizing a combination which will permit an effective drug still to be held in reserve for complications or spread, or to cover surgical intervention. Thinking along these lines, one would hesitate to use our two best agents, namely, SM and INH, simultaneously. Since the therapeutic results appear to be equal, it is considered preferable to utilize INH with PAS, or SM with PAS, thus leaving a potent agent in reserve. The next logical question is, Are three drugs even better than two, and should one routinely utilize SM-PAS and INH? A substantial amount of evidence has been accumulated that the administration of all three drugs together offers no advantage over giving only two, at least as regards roentgen clearing and conversion of sputum, and (on this aspect we have less information) the development of drug resistance.[5] At the present time, therefore, the only valid indication for the utilization of all three drugs, it is generally agreed, is tuberculous meningitis or miliary tuberculosis, and the use of all three, even in these grave conditions, is seriously questioned by competent authorities. There is no disagreement, however, that the use of INH, whether alone or in combination, is mandatory in the treatment of tuberculous meningitis or miliary tuberculosis, and that since this drug has become available the mortality from these manifestations of tuberculosis has shown a sharp decrease.

The next question is dosage and side actions and how to cope with the latter. It has been shown in a large statistical study that the administration of SM in doses of 1.0 gm. twice a week gives results at the third and fourth months which are in every way comparable to administering SM daily. The only difference observed has been that acutely febrile, toxic cases on daily therapy reach normal temperature levels more quickly, but the roentgenograms, bacteriologic results and clinical status after three to four months are identical in those receiving SM, 1.0 gm. daily, and SM, 1.0 gm. twice a week, with the decided advantage in the latter case that in cases presenting large, thick-walled cavities the emergence of resistant bacilli is definitely delayed by intermittent administration. A current tendency in acutely toxic and febrile patients is to give SM daily for one month, and then switch to intermittent. There has been much discussion as to whether one should routinely utilize SM or dihydrostreptomycin (DHSM). SM tends to cause greater damage to the vestibular apparatus when it is given for prolonged periods of time than does DHSM, and DHSM tends to produce more toxicity to the auditory nerve on prolonged administration than does SM. If one must have one of these complications, it is felt by most

that a mild degree of vestibular damage is preferable to deafness, particularly since the body mechanism tends to compensate and recover from vestibular damage, whereas the hearing loss in most cases is permanent and may not appear until after the SM or DHSM is discontinued. Both of these complications of SM-DHSM, according to recent studies,[5] can be reduced to an insignificant percentage by the combination of the two, utilizing 0.5 gm. of each, and where daily administration is necessary this combination (officially designated as streptoduocin, commercially Combistrep or Distrycin) is recommended. However, for intermittent administration there is a tendency by most to prefer SM, 1.0 gm. twice a week, in which the incidence of vestibular toxicity is very low and can generally be detected very early, and hearing toxicity even less. The utilization of either SM or DHSM, rather than the combination of the two on intermittent combined regimen, is also preferable from the standpoint of being able to make a frequent switch when allergic skin or other manifestations occasionally appear.

PAS is given concurrently with SM in a recommended dosage of 12.0 gm. of the free acid daily. It is important to emphasize that if one is using the sodium PAS salt it is necessary to give 16.5 gm. of the sodium salt to equal 12.0 gm. of the free acid. To overcome the gastrointestinal upsets due to PAS which are so common, particularly in the early weeks of its administration, a variety of dosage forms have become available, including buffered tablets, granules, effervescent tablets, and so forth. One must determine by trial and error which dosage form is best tolerated in the individual case. In general, by starting with a small dose and gradually increasing to the maximal dose, and the concurrent administration of such agents as aluminum hydroxide gel or belladonna or Thorazine, the great majority of patients, after the first two or three weeks, can continue taking the drug without significant difficulty. Fever, rash, hypoprothrombinemia, myxedema, asthma, severe hepatic disturbance, or a condition resembling infectious mononucleosis may occur as complications of PAS therapy, but fortunately in a very low percentage of cases.

INH is generally given in a dosage of 300 mg. daily, divided in three doses, for the average adult, with dosages three or four times this high in miliary tuberculosis or tuberculous meningitis. The utilization of INH has been remarkably free of significant toxic side effects except for peripheral sensory and apparently motor neuropathy, tending to occur in malnourished or alcoholic patients or at high dosage levels.

How long shall these drugs be given, and when may the target point of chemotherapy be said to be achieved? As for optimal duration of chemotherapy, the answer is that we really do not know. Recommended courses of therapy have increased from 40–60–90 and 120 days to the current eight to 12 months or longer. A recent investigator contemplates giving the drugs for life.[6] Talking to phthisiologists about the country at large, one gathers that the general tendency is to continue the drug regimen in those cases becoming "inactive," as defined above, for at least six months after

the inactive state has been achieved. In those cases where the inactive state is achieved as a result of surgical intervention, there is likewise a tendency to continue the chemotherapeutic regimen for from six to 12 months after the date of the surgical operation. In those cases remaining active who refuse surgery, or who are not suitable candidates for surgery, the continued administration of INH appears to be associated with a markedly lessened tendency towards roentgen progression or clinical deterioration, despite the persistence of positive sputum and INH-resistant bacilli. In what type of response can we be satisfied with drug therapy alone? Naturally the most hoped for and favorable response is the clearing of infiltrations to such an extent that nothing of significance is noted on the roentgenograms. Where this does not occur, or is incomplete, the appearance of linear and fibrotic-appearing lesions or nodular lesions of small size which remain stable for many months is considered to have the best prognosis. On the other hand, where cavities (and frequently good anteroposterior and lateral tomograms are necessary to demonstrate them) or solid large foci remain measuring perhaps 1 cm. or more, and particularly if these represent cavities which have filled in under therapy, the current tendency is to remove such foci, if at all possible, for fear that they will be sources of progressive disease at a later date. Whether this line of thinking is completely justified is being questioned and actively investigated by a number of groups; it is based on the demonstration that the bronchus draining a tuberculous cavity becomes epithelized, as a result of chemotherapy, at its junction with the cavity,[7] and that virulent tubercle bacilli can be cultured from residual, necrotic tuberculous foci resected after prolonged, combined chemotherapy.[8]

What is the rôle of bed-rest in the treatment of pulmonary tuberculosis today—formerly *the* medical method of treatment? The general feeling is that, until roentgen stability has been achieved, bed-rest is definitely helpful in accelerating the response. Since exudative lesions today tend to clear much more quickly under chemotherapy, and to become inactive more quickly, the over-all duration of bed-rest has, in practically all institutions, been greatly shortened. There are many who feel, and we are certainly inclined to agree, that a cheerful frame of mind and a relaxed attitude on the part of the patient are even more important than the adequacy of physical bed-rest alone, and certainly every attention should be given to the psychosomatic factors which are frequently so important in this chronic disease. This does not mean that one requires a psychiatrist, except in the occasional difficult case, the art of medicine as practiced by the physician in attendance being quite sufficient in the vast majority.

What is the rôle of medical collapse therapy today? Pneumothorax treatment has, in practically all institutions, just about gone into oblivion. The danger of pleural complications and, even in those cases where no pleural complications occur, the loss of pulmonary function resulting from a re-expanded, so-called uneventful pneumothorax, is considered too great a price to pay for the isolated cavity which in most cases today can be handled so

much better with either chemotherapy alone or, if healing fails to occur on chemotherapy, a limited amount of pulmonary resection or surgical collapse. Pneumoperitoneum, so popular five to six years ago, is also being used much less. The reason for this appears to be that for a long time this method was

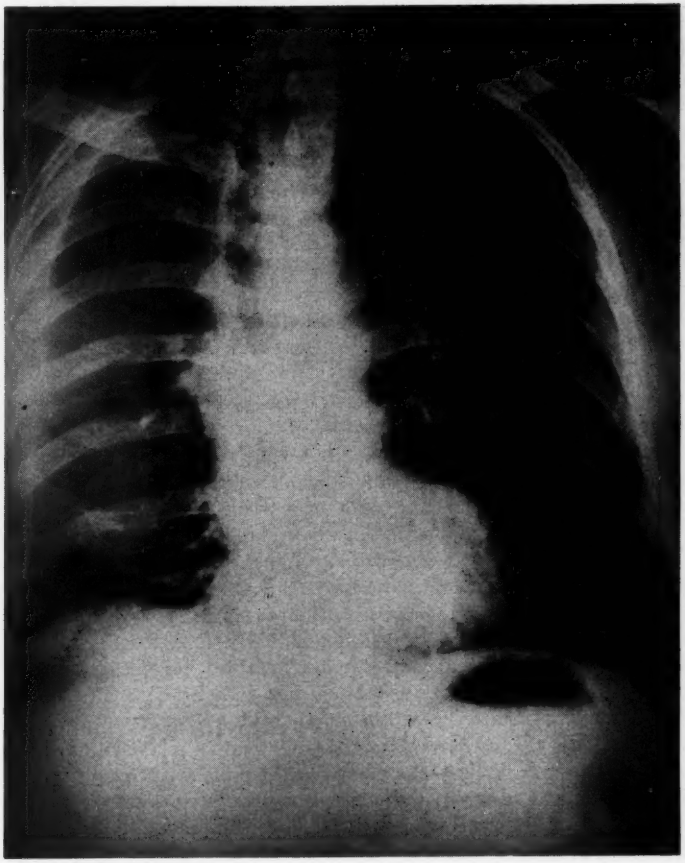

FIG. 1. Chest roentgenogram, 4–17–53, showing markedly thickened pleura. Sputum was positive. Cavity was demonstrated in superior segment of right lower lobe on right lateral tomograms, correlating with the findings noted at right "hilum" region on this film. Original treatment SM-PAS had been started 12–7–52. Right upper lobe free of demonstrable disease.

used rather uncritically, together with chemotherapeutic agents, and favorable results were ascribed to the combination. However, in the past few years, as we have been less impatient to start pneumoperitoneum, roentgen improvement has been noted to occur at the same speed and to the same

degree as in those cases that were previously given pneumoperitoneum plus drugs. Our current tendency, therefore, is to consider pneumoperitoneum when roentgen improvement on serial monthly films appears to have hit a plateau, and then to utilize it where cavities are small and thin-walled, or

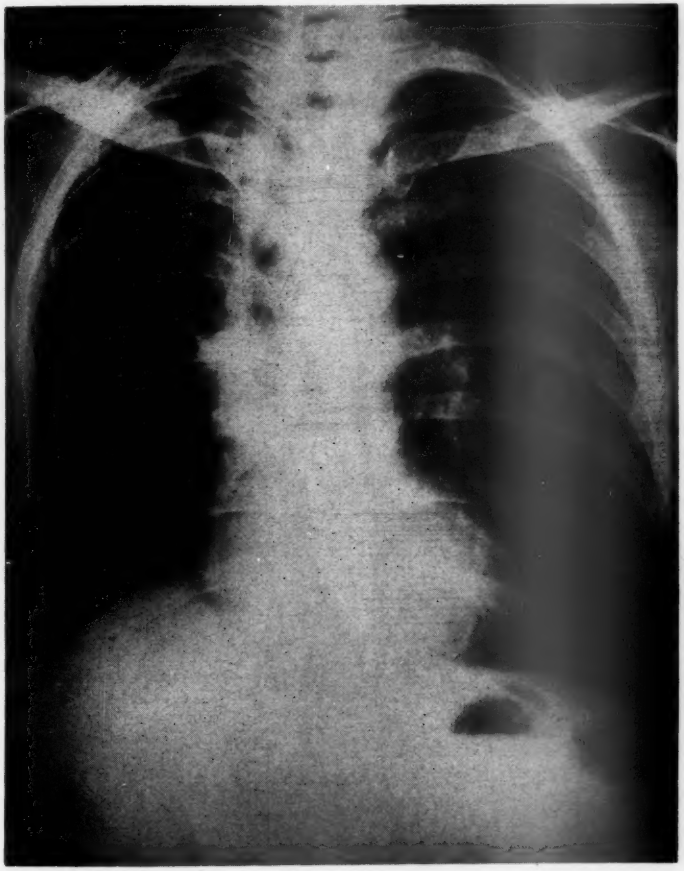

FIG. 2. Chest roentgenogram, 11–19–53. A definite infiltration with cavity is now seen in right upper lobe behind medial end of clavicle. At operation on 4–27–53, decortication and right lower lobectomy, no disease was palpable in the right upper lobe. SM-PAS had been continued without interruption, and sputum was negative postoperatively until this cavity appeared.

where small cavities are suspected because of the persistence of positive sputum, although not clearly demonstrated.

I should like to offer a final word of caution as to the growing tendency toward ambulatory treatment, and also to indicate a need for conservatism

and reserve regarding the ultimate results of long-term chemotherapy. As to ambulatory therapy, recent figures from the New York City Department of Health,[9] indicating no significant improvement on roentgenogram in 68% of the cases, and the persistence of positive cultures in 53% of the cases

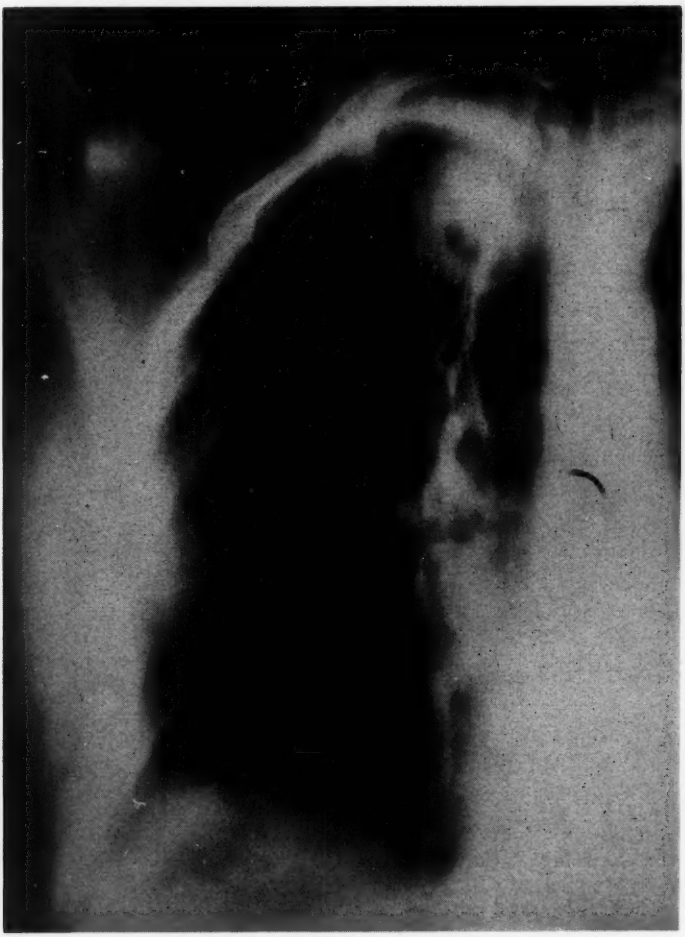

FIG. 3. Tomogram, 12–3–53, delineates right upper lobe disease and cavity better than conventional roentgenogram of 11–19–53. Patient had become resistant to PAS; INH was added to SM-PAS regimen on 12–18–53, and right upper lobe disease resected 5–17–54.

after six months of ambulatory chemotherapy, results which appear far inferior to those obtained with hospital regimen including surgery where necessary, certainly should make us wary despite favorable clinical appear-

ances. A note of caution also as to final evaluation of the results of long-term therapy, and to illustrate this point I should like to show the roentgenograms in one case. This patient received uninterrupted, long-term, original-treatment chemotherapy, a combination currently considered by many to be the "rabbit's foot" against progression and relapse; despite this, during the administration of this course of treatment, there appeared a fresh infiltrate which went on to excavation, with positive sputum after one year of such therapy (figures 1, 2, 3). We have seen several cases similar to this, and these occurrences, plus the demonstration of viable tubercle bacilli in closed lesions resected after many months of chemotherapy, make us wonder whether by chemotherapy we are not just achieving an exquisite retardation of the development and progression of tuberculous lesions, rather than a sterilization of these lesions, as is our hope at the present time. Should this prove to be true, even in a relatively small percentage of the patients now receiving long-term chemotherapy, we will be ill-equipped to handle the crop of late relapses in view of the present tendency to decrease tuberculosis beds and close tuberculosis sanatoria.

Summario in Interlingua

Con pauc exceptiones, omne caso active de tuberculosis pulmonar merita un longe ininterrumpite curso de chimotherapia combinate. Le factos nunc cognoscite pare indicar que del puncto de vista tractamental il non importa si on usa un regime de (1) streptomycina plus acido para-aminosalicylic o (2) hydrazido de acido iso-nicotinic plus acido para-aminosalicylic o (3) streptomycina plus hydrazido de acido iso-nicotinic. Nonobstante, del puncto de vista practic il existe un bon ration pro non usar streptomycina plus hydrazido de acido iso-nicotinic como regime del tractamento initial. Le disveloppamento de resistentia a iste duo drogas eliminarea ab le subsequente utilisation therapeutic duo del plus efficace agentes nunc disponibile. Nulle avantage pare resultar del utilisation simultanee de omne le tres drogas mentionate, excepte in le tractamento de tuberculosis miliar o meningeal, e le necessitate de utilisar le tres drogas assi in iste grave conditiones ha essite questionate.

Le duration optimal del regimes chimotherapeutic se trova sub investigation active. Al presente le practica currente utilisa le therapia antimicrobial usque a inter 6 e 12 menses post le attingimento del stato inactive, e iste methodo pare obtener melior resultatos a longe durantia que le relativemente breve cursos de chimotherapia que esseva in uso in le passato.

Cavitates que persiste in le curso del chimotherapia deberea esser attaccate per resection o collapso, sin reguardo al stato bacteriologic del patiente. Quanto al casos de remanente focos non-cavitari solide, le question del meritos comparative de resection e de therapia a drogas sin chirurgia es le thema de studios controlate. Al tempore presente on favori le resection de remanente focos solide si illos es in ulle senso de dimensiones considerabile. Iste attitude es basate principalmente super le factos (1) que on ha demonstrate le existentia de patente bronchos ducente a tal focos e (2) que le prolongate incubation in appropriate medios ha demonstrate le existentia in tal lesiones de viabile bacillos tubercular. On es generalmente de accordo que focos solide con diametros de plus que 2 cm representa un grave causa potential de relapso si illos non es subjicite al resection.

Pneumothorace ha essite abandonate plus o minus completemente proque illo involve un marcate sacrificio de capacitate pulmonar in le tractamento de un typo de lesion que es generalmente plus facile a attaccar per medio de un resection localisate.

Pneumoperitoneo es ancora in extense favor, sed multe experite phthisiologos questiona su ultime valor como methodo collapsional.

Le rolo de allectamento in le tractation de tuberculosis pulmonar durante un efficace regime de chimotherapia se trova sub studio critic. In general on opina que le allectamento es clarmente de valor durante le prime acute e toxic phases del morbo e probabilemente durante le phase del active resolution de infiltrationes. Del altere latere, relative al periodo post le attingimento de alicun grado de stabilitate on ha seriemente questionate le necessitate de prolongate periodos de stricte allectamento. Le duration general del stricte allectamento ha essite marcatemente abbreviate depost le utilisation de prolongate cursos de chimotherapia.

Il ha essite demonstrate que lesiones tuberculotic pote apparer, progreder, e resultar in cavitates durante un non-interrumpite curso de chimotherapia. Iste facto—insimul con datos colligite in re programmas therapeutic instituite per le Statounitese Departimento de Sanitate pro patientes visitante—deberea sufficer pro inseniar a nos un satis pronunciate conservatismo verso le crescente popularitate de chimotherapia ambulatori.

BIBLIOGRAPHY

1. Robins, A. B.: Tuberculosis in New York City today, Quart. Bull., Dept. of Health, City of New York, Winter 1953–1954, pp. 52–57.
2. Waring, J. J.: The current treatment of pulmonary tuberculosis, Dis. of Chest **25**: 361–373 (Apr.) 1954.
3. Walker, A. W., for the Veterans Administration Committee on Chemotherapy: The chemotherapy of tuberculosis in man, J. A. M. A. **147**: 253–258 (Sept. 15) 1951.
4. Karlson, A. G., and Feldman, W. H.: The effect of combined therapy with streptomycin and para-aminosalicylic acid on experimental tuberculosis in guinea pigs, Proc. Staff Meet., Mayo Clin. **24**: 510–515 (Sept. 28) 1949.
5. Transactions of the 13th Conference on the Chemotherapy of Tuberculosis of the Veterans Administration, Army and Navy, St. Louis, Mo., Feb. 8–11, 1954.
6. Dooneief, A. S., and Hite, K. E.: Indefinitely prolonged chemotherapy for tuberculosis, Am. Rev. Tuberc. **70**: 219–227 (Aug.) 1954.
7. Auerbach, O., Katz, H. L., and Small, M. J.: The effect of streptomycin therapy on the bronchocavitary junction and its relation to cavity healing, Am. Rev. Tuberc. **67**: 173–200 (Feb.) 1953.
8. Hobby, G. L., Auerbach, O., Lenert, T. F., Small, M. J., and Comer, J. V.: The late emergence of *M. tuberculosis* in liquid cultures of pulmonary lesions resected from humans, Am. Rev. Tuberc. **70**: 191–218 (Aug.) 1954.
9. Drug therapy in the management of the unhospitalized tuberculous patient, Scientific Exhibit of the Department of Health, New York City, at the Graduate Fortnight of Medicine, N. Y. Academy of Medicine, October 18–29, 1954.

EFFECT OF PHYSICAL METHODS ON THE MECHANICS OF BREATHING IN POLIOMYELITIS * †

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THE use of physical methods in the rehabilitation of patients with bronchopulmonary diseases stimulated our interest in the breathing difficulties of convalescent patients with respiratory involvement due to poliomyelitis. The application of certain physiologically established principles was shown to improve the aeration of the lungs in patients with pulmonary emphysema. Methods of increasing diaphragmatic excursion included the employment of the headward tilt of the thorax,[1] the application, in the supine position, of a weighted sandbag to the lower abdomen and, in the erect position, of an abdominal belt, of manual compression of the chest to assist expiratory emptying of the lungs, and active abdominal muscle strengthening exercises.[2] Mechanical means of eliminating retained bronchial secretions were used in the therapy of coöperative patients with chronic bronchitis or bronchiectasis, and some cases of pulmonary emphysema. Exsufflation with Negative Pressure (E.W.N.P.) appeared to be the most effective method available to achieve that purpose.[3] The successful application of these principles of physiologic therapy of bronchopulmonary disease to a patient with poliomyelitis [4] resulted in a wider trial of some of these methods in a group of poliomyelitis patients.

It is the purpose of this paper to report the alterations in the pattern of pulmonary ventilation in cases of poliomyelitis during inhalation of 100% oxygen, during (1) the application of a Gordon-Barach belt, (2) the application of a sandbag to the lower abdomen, and (3) the assistance of expiration by a maneuver of manual compression of the lower ribs.

The clinical application of E.W.N.P. will also be presented by means of case histories and a discussion of the indications and limitations of this mechanical method of eliminating secretions.

METHODS

Pulmonary ventilation measurements were obtained in 10 patients with chronic pulmonary insufficiency due to respiratory muscle paralysis second-

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‡ With the technical assistance of HARRY J. COSTELLO and WILLIAM H. SMITH, B.S.

ary to poliomyelitis by means of a Bennet Ventilometer, a specially valved gasometer, or a Benedict-Roth recording spirometer. The resistance to breathing through these devices was kept below 1 cm. water pressure during inspiration and expiration. In some subjects these measurements were repeated several times. Six of these 10 patients had ventilatory impairment of sufficient magnitude to require daily intermittent assistance of respiration by means of the rocking bed. One additional patient needed to return to the tank-type respirator occasionally to maintain adequate ventilation. The respiratory muscle involvement was moderate to marked in all patients, but slight diaphragmatic motion, either unilateral or bilateral, was present in all cases.

Ventilatory studies were carried out during the inhalation of air and 100% oxygen from the spirometer or an anesthesia bag serving as respiratory reservoir. Soda lime served as carbon dioxide eliminating method in the spirometer rebreathing system. The two other systems were of the non-rebreathing (open) variety. The deadspace of the systems was kept below 150 c.c.

In five patients the ventilatory effect of a double-spring type pad (Gordon-Barach) belt, applied to the lower abdomen, was determined. The minute volume of ventilation was similarly determined, with and without the application of a 10 pound sandbag on the lower abdomen of eight reclining patients. The response to a manually applied squeezing pressure to the lower ribs during the patient's spontaneous expiration was studied in 10 patients.

The effect of E.W.N.P. was observed during the treatment of 16 patients in whom difficulty in eliminating secretions due to respiratory involvement resulted in severe pulmonary and bronchial infections. The apparatus used in treating this group was previously described, including the Eliot Exsufflator * and the Cof-flator.[4] † The latter was found to be the more effective device in producing high flow rates and in clinical use,[5] E.W.N.P. was later found by Segal [6] to be effective in the evacuation of purulent sputum in cases of lung abscess, and by Williams and Holaday [7] in postoperative states. The Cof-flator type E.W.N.P. has also been successfully used for the elimination of retained secretions in cases of poliomyelitis by Affeldt [8] and Gordon,[9] and in pulmonary emphysema by Levine.[10] Gradual inflation of the lungs was produced by a motor blower unit, using a peak positive pressure of 40 mm. Hg at the end of a two to two and one-half second inspiratory cycle. This was followed by a pressure drop to 40 mm. Hg below the atmosphere in 0.02 second. The negative pressure was maintained for from one to two seconds. Flow rates of air produced by this rapid pressure drop of 80 mm. Hg were determined in 11 of these patients. Since the degree of the expulsion of air from the chest may vary when a mask or a

* This type is manufactured by the Eliot Medical Plastics Co., Lynn, Massachusetts.
† This model is made by O.E.M. Corporation, East Norwalk, Connecticut.

mouthpiece is used, or with a change in position of the patient from horizontal to that of a headward tilt of the thorax, flow rates were measured under these different conditions. A 5/8 inch orifice within a 7/8 inch tube, across which differential pressures were picked up by a Statham differential pressure transducer, was used as a pneumotachygraph. The differential pressures were recorded by means of Sanborn strain gauge amplifier on a Sanborn Visocardiette. A curve relating these differential pressures to flow rates had been obtained previously by experimental methods.

Experimental Results

The inhalation of 100% oxygen resulted in a moderate lowering of pulmonary ventilation when compared to breathing air in 13 instances, with an accompanying fall in the respiratory rate in all but three of the tests.

Table 1

Effect of the Inhalation of 100% Oxygen on Pulmonary Ventilation, Tidal Air and Respiratory Rate in Patients with Chronic Poliomyelitis

Case No.	Pulmonary Ventilation			Tidal Air			Respiratory Rate		
	Control Air c.c./min.	100% Oxygen c.c./min.	% Difference Oxygen -Air	Control Air c.c./ Breath	100% Oxygen c.c./Breath	% Difference Oxygen -Air	Control Air Breath/ min.	100% Oxygen Breath/ min.	Difference Oxygen -Air
1	7,620	5,650	−27	320	280	−13	23	20	−3
2	7,960	6,700	−16	400	370	− 8	20	18	−2
3	5,000	4,900	− 2	250	245	− 2	20	20	0
4	10,360	8,080	−22	470	405	−14	22	20	−2
5	7,190	6,370	−11	300	320	+ 6	24	20	−4
6	8,525	7,750	− 9	352	310	−12	30	25	−5
7	7,060	6,425	− 9	442	428	− 3	16	15	−1
8	5,300	5,000	− 6	190	194	+ 2	28	26	−2
9	7,350	7,120	− 3	460	445	− 3	16	16	0
10	6,900	6,720	− 3	328	292	− 5	21	23	+2
11	7,320	6,520	−11						
12	7,260	5,960	−18						
13	8,500	5,900	−30						
Mean			−13%			− 5%			−1.7%

The tidal air values were not significantly altered, as seen in table 1 and figure 1. The mean decrease in pulmonary ventilation was 13% when breathing 100% oxygen, the range varying from 100 to 2,600 c.c. per minute. The patients manifestly breathed with less effort, but no clinical signs of oxygen-induced respiratory acidosis, stupor or irrationality were observed during the seven minute testing period.

The application of the Gordon-Barach belt or a sandbag to the lower abdomen when the patients breathed air resulted in a decrease in the pulmonary ventilation in 11 of 13 determinations, with a mean decrease of 11%. In all but two experiments a decrease in respiratory rate and an

increase in tidal air occurred, as seen in table 2 and figure 1. Improvement in dyspnea was accompanied by a diminution of respiratory accessory muscle movement.

When the patient's respiration was assisted by manual compression of the lower chest during each expiratory cycle, an increase in pulmonary ventilation varying from 6 to 77% was achieved in eight of 11 determina-

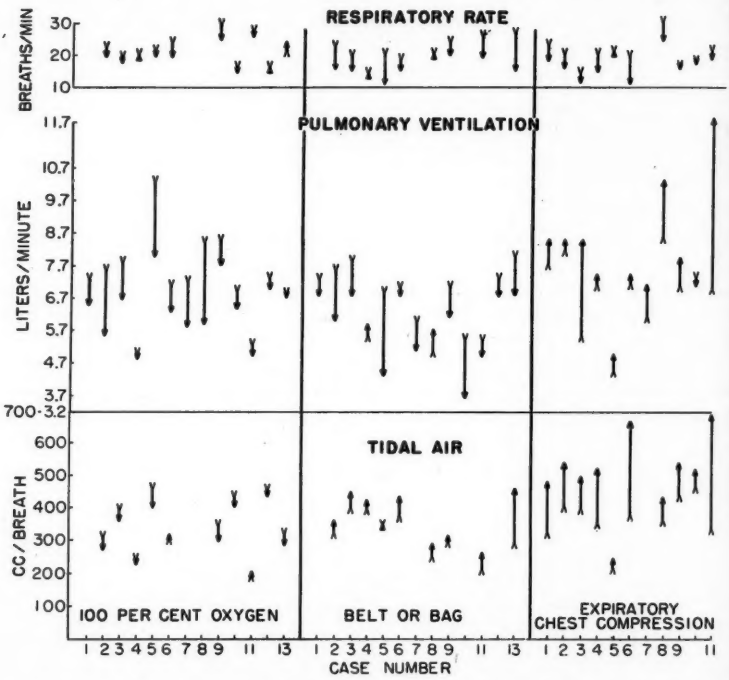

FIG. 1. The increased tidal air in the presence of a decreased minute volume of respiration and respiratory rate, when a bag or belt is applied to the lower abdomen of patients with respiratory insufficiency due to poliomyelitis, suggests a more efficient ventilatory gas exchange due to increased intra-abdominal pressure and greater utilization of the diaphragm than when oxygen is administered and a reduction in tidal volume occurs. The application of expiratory compression of the ribs accomplishes a still greater efficiency of ventilation, as indicated by an increased, but effortless, minute volume and tidal air.

tions. The remaining three patients did not show any significant change in minute volume of breathing. The average increase in the 11 cases was 16% over control values. In 10 of these patients a decrease in respiratory rate of from three to eight breaths per minute occurred. The tidal air was increased from 30 to 285 c.c., with an average increase of 40% during chest compression, as seen in table 3 and figure 1.

TABLE 2

Effect of Increased Intra-Abdominal Pressure by Sandbag or Belt Applied to Lower Abdomen of Patients with Poliomyelitis

Case No.	Pulmonary Ventilation			Tidal Air			Respiratory Rate		
	Control Air c.c. /min.	Bag or Belt c.c./min.	% Difference Control, Bag or Belt	Control Air c.c./ Breath	Bag or Belt c.c./ Breath	% Difference Control, Bag or Belt	Control Air Breath/ min.	Bag or Belt Breath/ min.	Difference Control, Bag or Belt
1	7,620	5,050	−20.5	320	355	+11	23	17	− 6
2	7,960	6,860	−13.8	400	430	+ 7	20	16	− 4
3	5,525	5,890	+ 6.5	395	420	+ 6	14	14	0
4	7,065	4,240	−40	350	350	0	20	12	− 8
5	6,125	6,940	− 2.7	375	430	+15	19	16	− 3
6	5,000	5,700	+14	250	285	+14	20	20	0
7	7,190	6,165	−14	300	310	+ 4	24	20	− 4
8	5,400	4,900	− 8	210	260	+24	26	19	− 7
9	8,070	6,865	−15	290	460	+58	27	15	−12
10	7,320	6,850	− 8.8						
11	6,035	5,180	−14						
12	5,550	3,600	−25.2						
13	7,260	6,720	− 7.8						
Mean			−11			+15			− 5

The effect of squeezing the lower chest during expiration on the ventilation of a patient with poliomyelitis is illustrated in figure 2. When nine patients were assisted in the completion of expiration by manual compression of the lower chest, significant increases in vital capacity occurred in six patients. The average increase in vital capacity for all nine patients was 27% as seen in table 4.

TABLE 3

Effect of Manual Compression Applied to Lower Thorax on Ventilation in Patients with Poliomyelitis

Case No.	Pulmonary Ventilation			Tidal Air			Respiratory Rate		
	Control c.c./min.	Manual Compression	% Difference Control -Manual Compression	Control Air c.c./ Breath	Manual Compression c.c./ Breath	% Difference Control -Manual Compression	Control Air Breath/ min.	Manual Compression Breath/ min.	Difference Control -Manual Compression
1	7,620	8,520	+17	320	475	+ .47	23	18	−5
2	7,960	8,520	+13	400	535	+ 33	20	16	−4
3	5,525	8,580	+ 6	395	490	+ 24	14	12	−2
4	7,065	7,225	+ 2	350	520	+ 48	20	14	−6
5	4,300	4,820	+12	215	245	+ 14	20	20	0
6	7,125	7,270	+ 2	375	660	+ 76	19	11	−8
7	8,525	10,250	+20	352	426	+ 21	30	24	−6
8	7,060	7,850	+11	442	530	+ 20	16	15	−1
9	7,350	7,175	− 2	460	512	+ 11	16	14	−2
10	6,900	12,200	+77	328	679	+108	21	18	−3
11	6,035	6,890	+14						
Mean			+16			+ 40			−3.7

Volume flow rates produced during the natural cough of 14 patients with poliomyelitis were in the case of 11 patients too small to be measured with any degree of accuracy on the pneumotachygraph available. In the remaining three patients the rates were above 3,000 c.c. per second. In 11

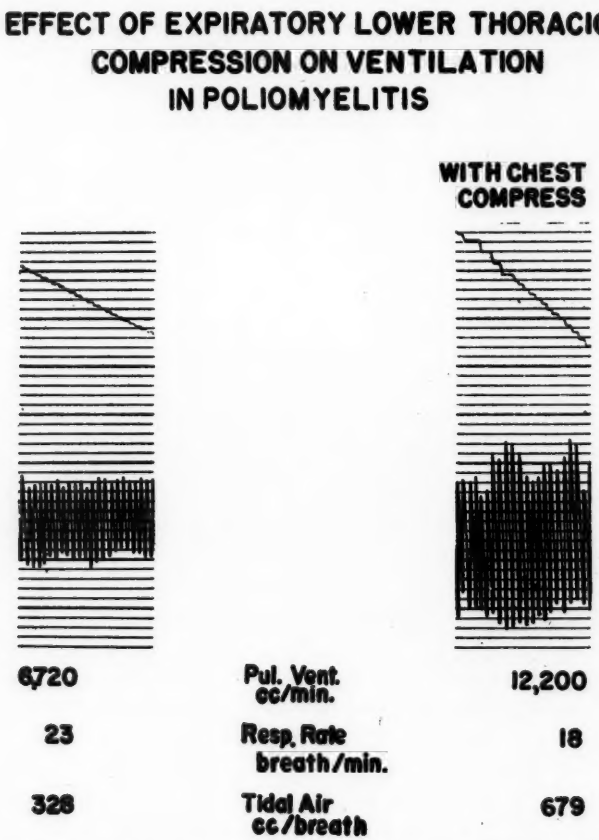

FIG. 2. A marked increase in minute volume of respiration and tidal volume of air, with a diminished respiratory rate, is produced during expiratory lower chest compression. The increase in tidal volume is produced mostly by an increase in the amount of air expired.

patients maximal expiratory flow rates during E.W.N.P. were considerably higher than those produced during their own natural cough, exceeding 4,330 c.c. per second, and averaging 5,460 c.c. per second. However, in three patients expiratory volume flow rates during E.W.N.P. were less than 3,000 c.c. per second, and apparently did not exceed those produced by

TABLE 4

Effect of Manual Compression Applied to Lower Thorax on Vital Capacities in Patients with Poliomyelitis

Case No.	Control	Vital Capacity (c.c.)	
		Manual Compression	% Difference
1	650	750	+ 16
2	850	900	+ 6
3	250	400	+ 60
4	1,100	1,150	+ 5
5	220	450	+102
6	425	500	+ 17
7	1,075	1,075	0
8	900	1,000	+ 11
9	1,075	1,310	+ 32
Mean			+ 27

their own natural cough. Two of the three cases could not be treated clinically by E.W.N.P. because of apprehension and lack of coöperation.

In 14 determinations of expiratory flow rates, comparing the differences between the mask and the mouthpiece and varying positions, e.g., erect, supine or headward-tilted position of the thorax, great individual variations occurred. In nine of these 14 determinations the flow rates were higher when a mask rather than a mouthpiece was used. Using a mask, the average expiratory flow rates were 470 c.c. per second higher than those recorded with the mouthpiece. However, it must be concluded from these experiments and clinical observations that both a mouthpiece and a mask might well be tried initially on a patient in whom the need of elimination of secretions by mechanical means arises. The device most convenient and comfortable to the patient is often found the most effective.

In five of seven patients, higher expiratory volume flow rates with E.W.N.P. were obtained in the head-down position than in the supine. It appeared as though the additional impact produced during expiration by the weight of the viscera upon the partially paralyzed diaphragm when the body was tilted headward served to augment the flow produced by the swift drop of pressure of E.W.N.P. in the majority of patients. Clinically, also headward tilting of the patient appears to increase the effectiveness of E.W.N.P. This may be explained in part by the increased expiratory flow rates and in part by the decrease in the slope of the trachea, which normally rises from the mid-portion of the chest mouthward at an angle of 16 degrees when the patient lies in the supine position.[11] This decrease in angle facilitates the mouthward propulsion of intratracheal secretions.

CLINICAL RESULTS

E.W.N.P. was used in 16 patients in whom respiratory insufficiency secondary to poliomyelitis was responsible for difficulties in elimination of

secretions. A course of treatment consisted of sessions of exsufflations or three to five "coughs" repeated at one minute intervals, six to 10 times, every one to two hours daily. Considerable care was taken to familiarize the patient thoroughly with the function and mechanical considerations involved in the use of E.W.N.P. When possible, the patient was shown the pressure dial and when inspiration and expiration could be expected, by indicating the swing of the needle to the positive and negative side of the gauge, respectively, when the mask or mouthpiece was occluded. Furthermore, the patients were instructed to permit the air to inflate the chest passively and to let it flow from the tracheobronchial tree without any expiratory effort on their part. They were also reassured that the procedure would be discontinued upon a predetermined sign given by the patients.

A detailed explanation of the entire process of mechanically induced coughing was found to be the single most important factor in obtaining the coöperation of the patient. The procedure was initiated in most cases by the use of low positive and negative pressures, e.g., plus 20 mm. Hg, minus 20 mm. Hg. During the first or subsequent sessions the pressures were gradually increased until the maximum of plus 40 mm. Hg, minus 40 mm. Hg was used. The mask was held firmly over the patient's face to prevent loss of pressure. For children, correspondingly smaller face masks were used. When the mouthpiece was employed, the patient was requested to close his mouth tightly around it; the nose was held shut throughout the procedure. The mouthpiece commonly used for basal metabolism determinations contained an oval metal tube insert which protruded three quarters of an inch from the portion placed between the teeth and lips; this metal insert was placed over the tongue, thereby preventing obstruction of the orifice of the E.W.N.P. tube by the tongue during the phase of negative pressure.

When large amounts of retained secretions were blown into the mouthpiece or mask during the first two or three exsufflations with E.W.N.P., the procedure was immediately discontinued and the face and attachments to the apparatus were cleaned. In many instances one or two exsufflations filled the patient's mouth with secretions, which were promptly eliminated by suction. This occurrence should be watched for. The patient may at times hold his breath in the expectancy of having the secretions removed from his mouth.

Closure of the glottis during E.W.N.P. is the most common cause for initial failure to obtain adequate eliminations of secretions. Absent or markedly diminished chest motion, or overinflation and deflation of the cheeks, are frequently good indicators of this situation. Reassurance of the patient and explanation of the need for unobstructed ventilation are used to overcome premature glottis closure.

Gastric overdistention is observed in isolated patients who are severely

ill and debilitated. Since this occurs because of the introduction of air into the stomach during the positive phase of E.W.N.P., when the swallowing reflex or cardiac sphincter of the stomach is involved in the primary disease process, the advisability of the introduction of a gastric tube (Levine tube) before the application of E.W.N.P. should be considered.

The coöperation of some patients may not be obtained for a variety of reasons: delirium, behavior problems due to encephalitic poliomyelitis, neuroses and negativism. In many of those patients E.W.N.P. cannot be used successfully. In patients with longstanding atelectasis, blood-streaked plugs of mucoid and mucopurulent secretions may be brought up after E.W.N.P. In our experience this is an excellent prognostic sign; relief of a long-standing obstruction may result in tearing of the mucous membrane to which the plug was adherent. Continuation of E.W.N.P. is indicated under these circumstances.

Case Reports

Case 1. A four year old girl was admitted to the hospital with the diagnosis of spinal poliomyelitis. She developed quadriparesis and was placed in a tank-type respirator on the fourth hospital day. Because of considerable respiratory distress during periods out of the respirator and the presence of secretions in the tracheobronchial tree, a tracheotomy was contemplated. However, a trial of E.W.N.P. was decided upon the fifth hospital day. Marked respiratory improvement occurred simultaneously with the elimination of large quantities of sputum and, four days later, she was placed in a crib and respiration was assisted by means of a chest respirator during the night.

Comment: E.W.N.P. may be used in very young children. Since their lung volumes are proportionally smaller than those of adults, the inspiratory and expiratory volumes may be diminished by reducing the inspiratory and expiratory times to one second and half-second, respectively. This procedure also increases the number of breaths per minute, which aids in the coughing of small children.

Case 2. A 37 year old woman, admitted to the hospital with spinal poliomyelitis, developed a quadriparesis and was placed in a tank-type respirator. She remained there for a month, when she was weaned in a chest-type respirator. Shortly thereafter she developed chest pain. The use of E.W.N.P. immediately resulted in the elimination of a large plug of purulent sputum, which was followed during subsequent treatments by smaller plugs of mucoid and mucopurulent sputum. The patient had a sensation of great relief and began to be able to breathe without the continuous assistance of a chest respirator. E.W.N.P. has been used since then whenever the accumulation of secretions became troublesome. She has been intermittently on a rocking bed since.

Comment: A dramatic relief of chest pain, dyspnea and apprehension, caused by the elimination of large amounts of secretions during E.W.N.P., was observed in this patient. To prevent recurrence of similar episodes of respiratory infection, patients of this type are advised to use E.W.N.P. in the form of intermittent maintenance therapy.

Case 4. A 33 year old male was admitted to the hospital with an encephalo-bulbo-spinal type of poliomyelitis. He was placed in a tank-type respirator. Because of persistent cyanosis a tracheotomy was performed, with good results as far as relief of cyanosis was concerned. However, several days later there seemed to be increasing dyspnea, and despite frequent suction elimination of secretions appeared to become an increasingly difficult problem. The use of E.W.N.P. resulted nearly immediately in a profuse elimination of secretions, which were aspirated with ease through the tracheotomy tube. Within 24 hours of initiation of E.W.N.P. the patient's response had been so excellent that he could be removed from the tank respirator and placed in a chest-type respirator.

Comment: The successful use of E.W.N.P. in a tracheotomized patient is illustrated by this instance. The tracheotomy tube was plugged during the procedure and E.W.N.P. was administered by means of a mask at the face. As soon as E.W.N.P. was discontinued, suction was performed through the unplugged tracheotomy tube.

Case 13. A 32 year old male, admitted to the hospital with spinal poliomyelitis, was placed in a tank-type respirator for one month. Following removal from the respirator for three days, he developed fever, marked dyspnea, cyanosis and difficulty in eliminating secretions. Although E.W.N.P. had been started, fever and dyspnea persisted, necessitating return to the tank respirator. When he was first seen by one of us, five days later, it was immediately noted that the patient held his glottis closed during E.W.N.P. He was then carefully instructed in the correct use of the apparatus. Following the first session of adequate mechanical coughing, a large mucopurulent plug of sputum was eliminated into the patient's pharynx and removed by suction. Immediately thereafter a marked outpouring of thin mucoid secretions from the tracheobronchial tree followed. Since suction had to be maintained continuously for 30 minutes following each session with E.W.N.P., and since his throat became markedly inflamed and irritated, it was decided to perform a tracheotomy for further suctioning following E.W.N.P. Since his neck was very short, the tracheotomy could not be used for the purpose of ventilation while he was in the tank respirator. After four days of combined use of E.W.N.P. to raise secretions to the level of the large bronchi and the tracheotomy tube for suctioning of the patient, he had improved to the point where removal from the tank respirator into a chest respirator was possible.

Comment: This patient's course illustrates the necessity for careful instructions accompanying the use of E.W.N.P. Closure of the glottis defeats any attempt to obtain high expiratory volume flow rates in the bronchi and trachea. The need for careful observation of adequate chest excursion during the use of E.W.N.P. cannot be sufficiently stressed. The sudden outpouring of mucoid sputum following the elimination of a single large purulent plug is a common observation after the initial use of E.W.N.P. If this becomes sufficiently marked to necessitate very frequent suction, the advisability of an accessory tracheotomy should definitely be considered.

Following this patient's recovery from his acute respiratory illness, expiratory volume flow and pressure curves were obtained experimentally, when E.W.N.P. was used by mask, with the tracheotomy tube occluded, and through the tracheotomy tube with the mouth shut and the nose clamped

(figure 3). Although the pressure curves obtained by the two methods were similar, the flow rates from the tracheotomy tube were found to be considerably lower than those recorded from the mask. This result may perhaps be explained by the relatively smaller orifice of the tracheotomy tube through which air had to be pulled, as compared to the lesser resistance encountered by the expiratory airstream through the trachea, pharynx and mouth. It had been our assumption that high expiratory volume flow rates were of great importance in the successful production of a mechanically induced cough, since they are the initiators of high air velocities within the tracheobronchial tree. The clinical impression gained prior to this experiment—that the use of E.W.N.P. directly through the tracheotomy was not quite so effective for the elimination of secretions as its use at the mouth with the tracheotomy tube occluded—appears to have been confirmed by this series of measurements.

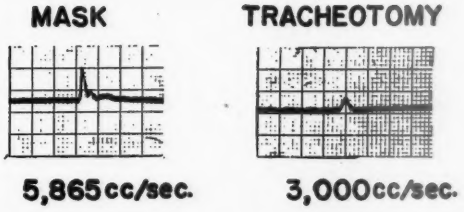

FIG. 3. Expiratory volume flow rates achieved during E.W.N.P., when applied through a tracheotomy tube and when the mouth and nose are occluded, are of a lower degree of magnitude than those obtained by mask or mouthpiece with the tracheotomy tube corked.

Case 15. A 29 year old spinal poliomyelitis patient had been dependent intermittently on a tank-type respirator for the last five years. Because of a period of prolonged residence in a respirator, and the possibility of a delay in weaning her from it because of dyspnea resulting from accumulated secretions, the use of E.W.N.P. was taken under advisement. Following the first treatment, throughout which the patient held her breath by closure of the glottis, she became markedly agitated, cyanotic and dyspneic. Although a careful explanation of the procedure preceded therapy, the patient's coöperation could not be enlisted and the treatments had to be discontinued. The patient remained in the respirator for a considerable period thereafter.

Comment: Lack of coöperation has been the greatest obstacle in the attainment of good results with E.W.N.P. in all cases. Fortunately, the number of patients whose coöperation cannot be enlisted is relatively small when care is taken to prepare them well before the procedure.

A summary of results in cases treated by means of E.W.N.P. is shown in table 5. In 13 of the 16 patients with poliomyelitis treated by E.W.N.P.

TABLE 5

Results of Treatment of Patients with Poliomyelitis by E.W.N.P.

Case No.	Age	Sex	Condition before Treatment	Duration of Treatment	Results of Treatment
1	4	F	Dyspnea, accumulation of mucus. In tank respirator.	4 days, q 2 hours.	Elimination of mucous plugs. Removed from respirator.
2	37	F	Chest pain, dyspnea, accumulation of secretions.	7 days, q 2 hours, later maintenance.	Subsidence of chest pain, elimination of one large mucous plug, followed by small plugs. Dyspnea relieved.
3	20	F	Dyspnea, accumulation of secretions. In tank respirator.	14 days, q 3 hours.	Dyspnea relieved. Removed from respirator.
4	31	M	Dyspnea, tracheotomy, accumulation of secretions. In tank respirator.	1 day, q 2 hours.	Elimination of large amounts of mucus. Removed from respirator.
5	27	F	Dyspnea, accumulation of secretions. In tank respirator.	2 weeks, q 2 hours.	Elimination of secretions. Removed from tank respirator.
6	7	M	Chest pain, accumulation of secretions, dyspnea.	2 days, q 2 hours.	Relief of dyspnea and chest pain.
7	39	F	Dyspnea, accumulation of purulent secretions. In tank respirator.	1 week, q 2 hours.	Relief of dyspnea, elimination of mucous plugs. Removed from respirator.
8	2	F	Chest pain, dyspnea, accumulation of secretions. In tank respirator.	2 days, twice daily.	Relief of chest pain and dyspnea, elimination of large amounts of secretions. Removed from respirator.
9	32	F	Dyspnea, accumulation of secretions.	2 days, q 3 hours.	Relief of dyspnea, elimination of large purulent and mucous plugs.
10	19	F	Fever, accumulation of secretions. Small area of RLL atelectasis. Vital capacity, 1,500 c.c.	5 days, q 4 hours.	Elimination of large purulent and mucous plugs. Subsidence of fever in 24 hours. Aerations of atelectasis. VC, 3,000 c.c. after 2 days E.W.N.P.
11	7½	M	Dyspnea, accumulation of secretions.	5 days, q 3 hours.	Elimination of mucoid secretions. Relief of dyspnea.
12	8	M	Dyspnea, cyanosis, accumulation of secretions. In tank respirator.	6 days, q 3 hours.	Elimination of mucoid secretions. Relief of dyspnea. Removed from tank respirator.
13	32	M	Dyspnea, cyanosis, fever, accumulation of secretions. In tank respirator.	14 days, q 3 hours.	Elimination of very large amounts of mucoid secretions. Tracheotomy to facilitate suction. Relief of dyspnea. Removed from tank respirator.
14	23	M	Dyspnea, marked cyanosis, loss of consciousness, tracheotomy, retained secretions.	4 days, q 2 hours.	Elimination of secretions; no relief of dyspnea and cyanosis. Death.
15	29	F	Dyspnea, accumulation of secretions. In tank respirator.	1 treatment.	Uncoöperative, hysterical, increased cyanosis. Procedure discontinued.
16	20	F	Following removal of kidney stones, dyspnea, accumulation of secretions.	1 treatment.	Uncoöperative. Patient refused further therapy with E.W.N.P.

the results were excellent. Improvement consisted mainly in elimination or reduction of dyspnea, cyanosis and chest pain, clearing of the signs of consolidation of the lungs or atelectasis, and elimination of obstructing mucous or purulent plugs. Of the 13 improved patients, E.W.N.P. contributed to a large extent to the discontinuation of the use of the tank-type respirator in eight. In two patients the presence of a tracheotomy did not only not interfere with the effectiveness of E.W.N.P., but also may have facilitated the problem of removal of secretions from the trachea by means of suction after they had been brought to that level from the smaller bronchioles by this mechanical means of coughing. In two of the three patients in whom E.W.N.P. did not produce good results, the failure was due to inability to enlist their coöperation during treatment. In the third patient, failure was due not to inability to clear the bronchial tree of secretions by means of E.W.N.P., but to marked cerebral anoxia following prolonged respiratory obstruction by secretions prior to the use of the device.

Discussion

Improvement in the efficiency of expiration by the use of pressure exerted on the lower abdomen by either a belt or a weighted sandbag or the headward tilt of the thorax in patients with chronic poliomyelitis resulted in decreased dyspnea and diminution of the use of accessory muscles of respiration. In a previous report [1] the arterial oxygen saturation, CO_2 tension and pH of patients with pulmonary emphysema were not adversely affected as a result of increasing the intra-abdominal pressure in this manner for an hour, although a marked lowering of the pulmonary ventilation, similar to that described in this report, occurred. An increase in the efficiency of ventilation was indicated by both the increase of the tidal volume and the diminished respiratory rate. These observations suggest that the therapeutic value of increasing the intra-abdominal pressure by the methods described (in these cases of chronic poliomyelitis) is related to correction of an inadequate expiratory ascent of the diaphragm. The augmentation of the minute volume of breathing by rhythmic compression of the lower chest during expiration indicated that a similar decrease in dyspnea could be produced by a procedure of this kind. This method appears to be of greatest advantage in those cases in whom motion of the diaphragm is so small that increasing the intra-abdominal pressure alone will not increase respiratory ventilation sufficiently.

Determinations of ventilation conducted during the prone pressure (Schafer) method of resuscitation [12] (which also depends on increasing the tidal volume during expiration) in eight dead but warm patients indicated that an average tidal volume of 300 c.c. per breath could be achieved by compressing the lower ribs in the obvious absence of an active inspiratory effort. Since an active inspiratory excursion is present in most patients with poliomyelitis, lower chest compression provides an additional ex-

piratory reserve volume to the spontaneously achieved tidal air. The increase in vital capacity by lower chest compression is similarly caused by the addition of this same expiratory reserve. This is graphically shown in figure 4.

The lowering of the minute volume of breathing during the inhalation of 100% oxygen is not accompanied by increased efficiency of ventilation, although dyspnea and cyanosis are diminished, since elimination of CO_2 is not enhanced. Patients with poliomyelitis behave, in this respect, very similarly to those with pulmonary emphysema. In the program described

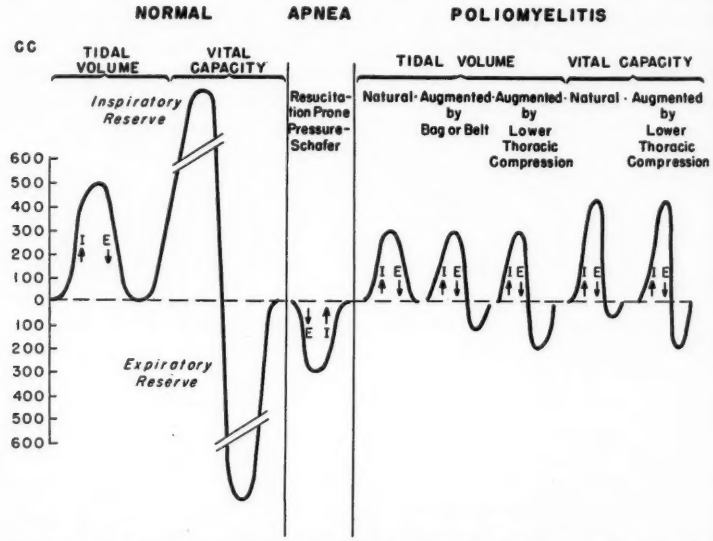

FIG. 4. An increase in tidal volume and vital capacity in poliomyelitis is produced by the application of a weighted bag or belt to the lower abdomen or lower thoracic expiratory compression. This increase is caused by enhanced expiration (utilization of the expiratory reserve) similar to that produced by the Schafer Prone Pressure method. The 0 line on the graph represents the resting and expiration position of the chest.

by Barach [13] for the management of emphysematous patients, oxygen therapy is used with gradually increasing concentrations of oxygen by "double bent nasal catheters"; specifically, a daily increase in oxygen flow by 1 L. per minute per day until 6 to 8 L. per minute are reached. In this manner, respiratory acidosis, resulting from sudden marked depression of the minute volume of respiration by high concentration of oxygen in the inhaled air, has been avoided in his series of cases, as well as in those of Simpson [14] in England. To some extent, similar considerations apply to the chronic poliomyelitis patient, although comparable studies on retention of base and increased chloride excretions have not been made.

The usefulness of Exsufflation with Negative Pressure (E.W.N.P.) in the elimination of secretions retained in the bronchial tree in poliomyelitis patients is enhanced by the fact that passive inflation and deflation of the chest are most easily achieved when the chest and diaphragmatic musculature are weakened as a result of neurologic involvement. The raising of secretions appears to be accomplished with great readiness in these patients during E.W.N.P., since often only two to three swift mechanical exsufflations are necessary to raise them into the mouth or oropharynx. Physiologic studies conducted during E.W.N.P.[15] revealed increased diaphragmatic motion, a slight increase in venous pressure, an increase in intragastric pressure, which is only slightly higher than that produced by hyperventilation, and no significant changes in heart rate or electrocardiogram. Hyperventilation occurs during E.W.N.P., and it was therefore used as a method of decreasing CO_2 retention and respiratory acidosis.[7]

These studies have indicated that the cardiovascular effects of this positive-negative pressure-breathing device are of such a nature that the device may be, and has been, safely used in extremely ill patients with poliomyelitis and other conditions such as postoperative lung complications, severe peripheral vascular collapse, coma or pulmonary edema. The automaticity of the device permits operation in the absence of spontaneous respiratory effort.

It is this automaticity, however, which is responsible for the inability manifested by some conscious patients to use E.W.N.P. Their inability to yield passively to the inspiratory and expiratory volume leads to failure of the device in its primary purpose of eliminating bronchial secretions. Conscientious instruction and careful explanation of the application of the methods are the best means of overcoming this obstacle.

In some unconscious patients (although in none of this series of cases), air may enter the stomach during the positive-pressure, or inflation, phase. The introduction of a gastric tube throughout the period of time during which the procedure is contemplated will alleviate this complication. The use of E.W.N.P. through an endotracheal tube has been very successful in a few patients with conditions other than poliomyelitis and has greatly facilitated endotracheal suction. However, the high incidence of irritation of the larynx following recovery has discouraged further use of this accessory in poliomyelitis cases.

Tracheotomy, although not necessary in the majority of patients, is not a contraindication to the use of E.W.N.P., nor does E.W.N.P. exclude the possibility of having to institute a tracheotomy to facilitate tracheal suction. It appears from our studies of expiratory volume flow rates that the use of E.W.N.P. in this instance is more effective when a mask is used over the face and the tracheotomy is corked than when the procedure is performed directly through the tracheotomy tube. The E.W.N.P. has,

however, greatly decreased the necessity for doing either tracheotomy or bronchoscopy to keep the trachea clear of secretions.

Although Whittenberger [15] has acknowledged that E.W.N.P. may be of value in patients with poliomyelitis who cannot cough, he remarks that it is no better than a good natural cough, and that the effectiveness of E.W.N.P. is dependent to a large extent on the previous inspiratory inflation of the lungs. The studies carried out in our clinic revealed that the twofold dilatation of the smaller bronchi was an integral part of the mechanism of eliminating retained mucin Thorotrast and bullets from the lungs of anesthetized dogs.[16] The virtue of inducing pulmonary distention by an inspiratory pressure of 30 to 40 mm. Hg includes not only the opportunity of passing air into previously unventilated alveoli beyond obstructing mucous plugs, but also storing relaxation energy in the inflated chest and enhancing the pressure drop from the bronchi to the lungs in the negative phase.

Since patients with bronchiectasis do not generally possess a "good cough," postural drainage has been used to eliminate bronchial secretions retained after the patient's apparently vigorous coughing efforts have been fruitless; similarly, E.W.N.P. has been added to the therapeutic procedures employed in bronchopulmonary disease to facilitate movement of mucus or pus from the bronchi to the mouth in precisely those clinical entities in which respiratory function is impaired by the ineffective, although frequently loud, cough.

In our clinic alone, including dispensary, office and hospital practice, E.W.N.P. is administered at a current rate of 3,000 treatments a year. Evidence of harm from its use has not been observed by us or reported from the other clinics where it has been in use.[3]

In many cases of bronchopulmonary disease the efficiency of ventilation has been found to be increased by augmenting the degree of movement of the diaphragm. As shown in previous reports,[4, 17] E.W.N.P. contributes greatly to an increase in diaphragmatic excursion, which aids effective aeration of hilar and lower lobe alveoli and thereby enhances elimination of secretions. Prevention of the common respiratory complications of patients with chronic poliomyelitis may be facilitated by measures that promote a better ascent of the diaphragm, i.e., the use of a lower abdominal belt, a weighted sandbag, lower thoracic compression and encouragement in the training of diaphragmatic breathing.

Summary

1. An increased efficiency of ventilation in patients, with a concomitant decrease in dyspnea and a lessened use of the accessory muscles of respiration, was obtained in seven of 10 patients with chronic pulmonary insufficiency due to poliomyelitis by increasing the intra-abdominal pressure. A sandbag and the G.B. belt placed over the lower abdomen were among the most effective measures used to raise the diaphragm into the chest. A more

effective ventilation of the hilar and lower regions of the lungs was manifested by a decreased minute volume of ventilation and increased tidal air.

2. An increased ventilation with a higher tidal air was produced by manual compression of the lower ribs during expiration.

3. Exsufflation with Negative Pressure was successfully employed in 13 of 16 patients with chronic poliomyelitis. The patients' own cough mechanism in these instances was not adequate to eliminate their retained secretions. The usefulness of this method in the presence of a tracheotomy is described. The failure of E.W.N.P. in three cases was due to lack of coöperation in two and to severe cerebral anoxia in one.

4. A gastric tube inserted prior to treatment with E.W.N.P. is used to prevent gastric distention in comatose patients.

5. A comparison of the use of a mask and mouthpiece with E.W.N.P. revealed marked individual differences, both clinically and experimentally, but no consistent over-all trend. It is recommended that both devices be tried in each patient initially, and that the one be used which achieves best results and is most comfortable for the patient.

SUMMARIO IN INTERLINGUA

In 7 ex 10 patientes con chronic insufficientia pulmonar debite a poliomyelitis, un augmento del efficacia ventilatori e un concomitante reduction de dyspnea como etiam un diminuite uso del musculos accessori del respiration esseva obtenite per methodos destinate a augmentar le pression intra-abdominal. Le application de un sacco de arena o de un cinctura de Gordon-Barach al abdomine inferior del patiente elevava su diaphragma a un position plus expiratori e resultava in un plus efficace ventilation del regiones hilar e basal del pulmone. Isto esseva manifeste in un reducite volumine-minuta e un augmentate volumine per respiration. Le compression manual del costas inferior durante le expiration resultava in augmentate ventilation con augmento del volumine per respiration. In 16 patientes con disturbate mechanismos ventilatori e tussitori debite a poliomyelitis, exsufflation con pression negative—un methodo pro le induction mechanic de tusse—esseva usate pro promover le elimination de accumulate secretiones. Un marcate melioration—manifeste in le grado de reduction del dyspnea, del cyanosis, e del dolores thoracic—e le disparition de signos de atelectasis esseva effectuate in 13 patientes. Le methodo non succedeva in 3 patientes, principalmente in consequentia de insufficiente collaboration del parte del patientes mesme. Le presentia de un tubo tracheotomic non interfere con le efficacia del technica de exsufflation con pression negative, providite que le apparatura es applicate per medio de un masca o pecia buccal e que le tubo tracheotomic es corcate. Es a recommendar que ante le application del technica a exsufflation con pression negative un tubo gastric es inserite in le caso de patientes comatose. Le preferibilitate del uso de un masca o de un pecia buccal debe esser determinate in cata caso individual secundo criterios de efficacia e conforto pro le patiente.

BIBLIOGRAPHY

1. Barach, A. L., and Beck, G. J.: The effect of the head-down position in patients with pulmonary emphysema, Am. J. Med. 16: 55 (Jan.) 1954.
2. Schutz, K.: Muscular exercise in treatment of bronchial asthma, New York State J. Med. 55: 635 (Mar.) 1955.

3. Barach, A. L., and Beck, G. J., with Spanier, M.: Exsufflation with negative pressure. Physiologic and clinical studies in poliomyelitis, bronchial asthma, pulmonary emphysema, and bronchiectasis, Arch. Int. Med. **93**: 825 (June) 1954.
4. Beck, G. J., and Barach, A. L.: Value of mechanical aids in the management of a patient with poliomyelitis, Ann. Int. Med. **40**: 1081 (June) 1954.
5. Beck, G. J., and Barach, A. L., with Smith, W. H.: Technic of employing exsufflation with negative pressure: a mechanical method of eliminating retained bronchial secretions, Mod. Hosp. **82**: 96 (Jan.) 1954.
6. Segal, M. S., Salomon, A., and Herschfus, J. A.: Alternating positive-negative pressures in mechanical respiration: the cycling value device employing air pressures, Dis. of Chest **25**: 640 (June) 1954.
7. Williams, E. K., and Holaday, D. A.: The use of exsufflation with negative pressure in post-operative patients, Am. J. Surg., to be published.
8. Affeldt, J. E.: Recent advances in the treatment of poliomyelitis, J. A. M. A. **156**: 12 (Sept. 4) 1954.
9. Gordon, C.: Personal communication.
10. Levine, E. R.: Personal communication.
11. Galloway, T. C., and Seifert, M. H.: Bulbar poliomyelitis, J. A. M. A. **141**: 1 (Sept. 3) 1949.
12. Gordon, A. S., Fainer, D. C., and Ivy, A. C.: Artificial respiration: report of the Council on Physical Medicine and Rehabilitation, J. A. M. A. **144**: 1455 (Dec. 23) 1950.
13. Barach, A. L.: Treatment of nontuberculous pulmonary disease, J. A. M. A. **156**: 1563 (Dec. 15) 1954.
14. Simpson, T.: Acute respiratory infections in emphysema, Brit. M. J. **1**: 297 (Feb. 6) 1954.
15. Whittenberger, J. L.: Artificial respiration and its clinical application, Seminar (Sharp and Dohme) **17**: 20 (Spring) 1955.
16. Bickerman, H. A.: Exsufflation with negative pressure (E.W.N.P.); elimination of radiopaque material and foreign bodies from bronchi of anesthetized dogs, Arch. Int. Med. **93**: 698, 1954.
17. Beck, G. J., and Scarrone, L. A.: Physiological effects of exsufflation with negative pressure, Dis. of Chest, to be published.

THE PSYCHOSOMATIC SEMINAR AS A MEANS OF CONTINUED CONSULTATION TO PHYSICIANS*

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Discussions with internist and general practitioner friends about the handling of difficult psychosomatic patients have led me to talk with them about how such problems are handled in seminars at a university hospital † with medical residents. Each physician with whom I have talked has indicated his feeling that such regular seminar discussions with a psychiatric consultant would greatly facilitate his work with patients. At this writing such a group has not been formed, but a local psychosomatic society is considering the possibility of such continued group discussions as a part of their program. The response of physicians to such an idea has prompted me to describe how such a seminar functions. The primary purpose of such meetings might be to help the physician to understand and work through difficult physician-patient relationships which are common with patients whose severe psychosomatic disorders give evidence of the gravity of their personality problems.

Some of my psychiatric colleagues have told me of their experiences in consultation with physicians who are having difficulties with a psychosomatic patient. Such consultations occur around crises in the treatment of the patient and are usually continued only as long as there is acute need for help. The use of psychiatric consultation to the physician on a regular basis is rare. I understand that Dr. Maurice Levine, of Cincinnati, holds an informal seminar for interested physicians.‡

I will try to describe some of the problems which confront the medical resident working with psychosomatic patients, and how the internist in charge and the psychiatric consultant collaborate in their effort to help the resident. The seminar is attended by three to six of the house staff assigned to the psychosomatic clinic for several months and those residents who, out of their own interest in certain psychosomatic patients, continue to follow them after their service in the psychosomatic clinic.

I should like first to describe briefly some of the kinds of patients the resident sees, the problems in management he often encounters, and the rôle of the internist and psychiatrist as consultants. Then I would like to generalize a bit on the difficult aspects of the relationship between psycho-

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‡ Personal communication from Dr. Robert Credé.

somatic patient and physician, and how the seminar may be of help to the resident in these problems.

Many of the patients seen in the psychosomatic clinic seem to be women past their middle forties. They are often overweight, and they complain of multiple aches and pains ranging from the head, back, chest, abdomen and pelvis to the extremities, sometimes all combined in one patient. Many of these women are unmarried and live alone. The married women appear unhappy in that relationship. Most of these women are isolated and have few friends. Many have had numerous contacts with physicians over a long period of time; they have received symptomatic treatment for their complaints and have finally been told that they were suffering from nerves, that their ailments were imaginary, or that the doctor felt they ought to have some special investigation to be found only at such a "wonderful place as the incomparable University Clinic." Thus many patients came to the clinic looking for the final answer to their ills.

A careful history and physical and laboratory examinations usually reveal little organic disease except for the obesity. As usual, these patients almost defiantly maintain that they "really eat very little." Exploration into the patient's background often reveals difficult and unsatisfying childhood relationships with the parents, and maladaptation to many life situations in school, socially and in employment. It usually becomes clear that the patient forms very tenuous relationships with both women and men, and has few friends and little contact with relatives.

The resident assigned to such a patient sometimes seems somewhat annoyed at having drawn an "old crock." He rarely says this aloud. After he recounts the history and physical findings, he may look about with a "Now, what do you expect of me?" expression. Frequently the internist and psychiatrist speculate together about the patient—Why does she come to the clinic now? What is she looking for in the relationship with the doctor? What kinds of physician-patient relationships has she experienced before? How has she unconsciously engineered rejection in that relationship before, etc.? We talk about why only a physician might be of help to her, and discuss at length how difficult and discouraging such patients are to work with. Often we compare the doctor's job in helping to keep in compensation the cardiac, arthritic or diabetic patient with the problem of helping such a psychosomatic patient function better, work, care for her needs and perhaps to need less intensive contact with the physician. Often at the end of such a discussion the resident agrees to attempt treatment of such a patient for his own experience, especially since he has heard that the senior members of the group are aware how difficult such patients are to work with.

We have found that the person whose need for attention and concern from other human beings is evidenced by manifold somatic complaints is often unable to accept referral to a social agency. Her physical symptoms

are unconsciously the only vehicle for obtaining contact with authoritative parental figures in the persons of doctors. The physician who can take the time and has the interest may be surprised by the kind of life adjustments these people can make with maintenance contact and interest from the doctor. The many demands, the hostility and marked dependency forthcoming from such patients may be difficult for the physician to live with and often may be the reason for the disruption of the work with the patient. We will discuss some aspects of these difficult relationships presently.

In the psychosomatic seminar we may see the patient who complains of bizarre physical symptoms. Although both men and women present such symptoms, often these men are in their thirties. They complain of terrible body odors which cause people to shy away from them or tease them, of germs crawling all over their bodies, or of feelings that the germs migrate from organ to organ. Their saliva is full of terrible bacteria which they spit up, and they cough up germ-laden material. Some feel their blood drained from them, and hot or cold fluids flowing from side to side. There are strange, awful feelings and shooting pains in head, back, abdomen and rectum. Many complain of feeling unreal, and state that they are certain something is rotting inside them. The physician who sees this patient instantly feels that he is dealing with a very sick person. These people are often alone, without family or close friends, and are marginally employed. It is usually difficult to obtain a coherent history; often these strange symptoms are of long duration, and sometimes the acute exacerbation of symptoms results from a recent disruption of a close relationship with wife, or a male or female friend.

Not infrequently the childhood history reveals serious disruption of the family early in the patient's life, or a history of seriously disturbed, isolated parents from whom the patient always felt estranged. Many such patients recall their own isolated, fearful, withdrawn feelings early in childhood. The physical and laboratory examinations frequently reveal no evidence of somatic disease, although occasionally peptic ulcer, asthma and lower bowel disturbances are found. When such patients are presented the resident turns quickly to the psychiatrist for confirmation that this is indeed a very disturbed, perhaps psychotic person. The physician indicates his anxiety about working with such a patient lest his lack of psychiatric training and experience precipitate an acute psychosis.

The psychiatrist may then help the resident consider the alternatives for this patient. He usually will not accept referral to a psychiatric clinic, and may even become quite disturbed at the suggestion, both because of the implication that he is crazy, and the feeling that the doctor to whom he has come for help and understanding is sending him away. The consultant's own experience has been that such patients may be helped considerably by attentive, patient listening without any probing, pushing or interpretation, and that such an attitude on the doctor's part will not pre-

cipitate an acute psychotic episode. Thus he usually encourages the resident to try to work with the patient in this way, with weekly progress reports to the seminar. The internist recounts his own experiences with such patients, and adds his conviction that a non-psychiatrist can work with such patients with consultation. He also stresses the reassuring aspects of a very careful physical examination and serious consideration of the physical symptoms. The work with such patients is often self-limited. The patient uses the relationship with the physician for a varying span of time to tide him over a difficult period. He begins to feel better, less disturbed, the bizarre symptoms recede, and if he finds a new, sustaining relationship elsewhere he may stop coming to the clinic. When this new relationship is disrupted he may return. The resident learns from this experience how he may be of some help to very disturbed people who will not accept referral elsewhere. He also learns that, in instances where the patient is very ill emotionally, where the impulse may be to jump in and actively do something to help such a person, he can be most helpful by his attentive and concerned listening and by gently helping the patient to talk.

Occasionally careful examination of a patient with such bizarre complaints will reveal serious somatic disease. It then becomes important to help the resident to focus on both the serious emotional and the somatic illnesses. In one instance it was only the interested and concerned attitude of the resident that made it possible for the first time to do careful physical and laboratory examinations of a very disturbed and suspicious woman. A severe diabetic condition was then uncovered which required careful and gentle psychologic handling to help the patient maintain the diet and medication. The resident who has been helped to work with so disturbed a person, to listen, even though anxiously at first, to the incoherent, strange and bizarre talk, to observe the odd behavior, and to begin to see the troubled human being beneath, whose feelings he can begin to understand, even a little, has had an important experience for his future work.

The last patient I would like to mention is the "interesting classical" psychosomatic patient, the person who suffers with peptic ulcer, asthma, migraine, obesity, rheumatoid arthritis, ulcerative colitis, etc. The resident feels that these patients are the kind he should be able to help in the psychosomatic clinic. With the patients previously discussed, the medical resident can accept the idea of attentive listening, and feels less impelled to do something. With these patients, however, he feels he should be able actively to help them understand and accept the emotional aspects of their illness and to uncover and pursue vigorously the various etiologic factors until the patient is cured. There is often resistance to the suggestions of both the internist and the psychiatrist that such probing and interpretation may not be helpful and that the desired results may not be forthcoming. Each resident must experience for himself that the dynamics of each illness as described in many textbooks cannot be usefully interpreted to the patient.

After some initial disappointment, many of the residents are better able to understand the kinds of early disturbed parent-child relationships which are important in the illness, and the rôle of the therapist who provides a new and corrective relationship, slowly and over a long period of time. They begin to accept the idea that the relationship between doctor and patient is the most vital aspect of the healing process. Uncovering and interpretation are finally understood as much less important in such treatment and, in fact, often detrimental if actively pursued.

This brings me to some remarks on the difficulties inherent in the physician-patient relationship with all the above kinds of patients. It is probably always true that the psychosomatic patient has lived through a malintegrative experience with his parents of such severity as to cause more or less serious personality disturbances. Most investigators would agree that these patients are seeking a better life adjustment through some more satisfying interpersonal relationship which might be more integrative than the difficult parent-child relationship they have experienced. Thus it becomes important for the physician to recognize and understand the rôles the patient places him in. In our experience the physician feels considerably easier and works more effectively with his patient as he begins to understand that the feelings of hostility, dependence, demandingness, love, sex, etc., are not aimed at him as a person, but as a representative—in the present—of important figures out of the patient's past. In the seminar, after a resident has worked with a patient for some period we can often begin to speculate, from both the historical data about early relations with parental figures and the way in which the patient-doctor relationship has developed, the kinds of problems the resident may encounter. Discussion and anticipation of these problems may be of help. Perhaps one of the most difficult aspects of work with psychosomatic patients is their incessant, hostile demands that the physician do something *now* about some acute anxiety or tension manifested somatically. The physician faces the dilemma of responding to the demands solely with symptomatic medication, which he knows will not be very helpful, or of encouraging the patient to express all his thoughts and feelings in words which might be relieving to the patient but difficult for the physician to listen to. Often the compromise of offering symptomatic medication if the patient must have it, but encouraging verbal expression of the feelings, is most effective. It is difficult, at the moment of being verbally attacked by a patient one is trying to understand and help, to recognize that the patient has placed the doctor in the rôle of the rejecting, depriving parental figure to whom he can now, in this more secure relationship for perhaps the first time, openly express hostile, demanding feelings. These demands can often be seen in retrospect as the hostile asking for that which was felt not to have been received from parents in childhood. If one observes the patient closely during such expression of rage, hostility and demandingness one can often note the

darting glances at the physician to see how he is taking the ventilation of such feelings. The patient is usually considerably relieved afterwards, both because the doctor has been able to accept the expression of such feeling without undue anxiety, and because their childhood fears that to express such feelings would result in some magical destruction of the person towards whom it was directed, or that the retaliation for having such feelings would destroy the patient, have been proved baseless. The patient usually trusts the doctor more after such an episode, and begins to be more convinced that someone can accept, and try to understand with him, all these "terrible" feelings and thoughts which he has inside.

The adoring, loving and sexual feelings that patients express may be just as difficult for the physician to feel comfortable with. It is often more difficult to recognize that one is a stand-in for significant people in the patient's past when such flattering, idolizing feelings (which most of us, as human beings, enjoy hearing) are expressed. The expression of intense feelings of love, of desire for sexual contact or of childlike dependence also tests the physician's capacity to accept the verbalization of such feelings without any rebuff, or response to the patient's invitation to be sexual partner or parent and take over the life of the patient.

It becomes increasingly important that the physician begin to recognize that, as a human being, he also has feelings different from his patient's only in their intensity and the degree to which they are disturbed and produce conflict. This awareness of the feelings common to human beings may make the patient's feelings, however bizarrely expressed, more comprehensible and easier to deal with. It might also make it easier for the doctor to understand and be less anxious about the kinds of feelings patients evoke in him. Since all of us out of our own past experiences have certain unresolved problems, we can expect that patients who express feelings in these, our own tender areas, will produce increased discomfort in us. An awareness of these inevitable tender spots in the physician may help him feel less tense when they are impinged upon by the patient's problems, and also more understanding of the patient.

As physicians, we learn early to present to the patient a picture of the calm, judicious, imperturbable, benign doctor. Many patients seeking the human underneath will probe, push and tug at this physician's armor until they find some chink which permits them to see the doctor as a human being. Thus the physician who can permit himself to admit fallibility, unsureness about certain things, and even his errors, may find that the patient seems to need to attack him less and seems easier with him.

To this end, in the seminar both the internist and the psychiatrist make every effort to discuss the kinds of feelings the patient may evoke in the resident, and to illustrate the possible reactions of the doctor to the patient from a free discussion of their own experiences. The resident is encouraged to relate how he feels about the patient and how he reacts to the patient so

that he learns to see that his own reactions are important and can be understood and shared with others. He may even learn something about both himself and his patient if he can discuss these feelings.

One of the most helpful aspects of such discussions is that the resident understands his patient better and feels more relaxed himself. He begins to see both his patient and himself as human beings, and he expects less of himself and needs to do less probing, pushing or interpreting in an effort to feel more effective or to disguise his own uneasiness with the patient. As this occurs, he can listen more objectively and can try to understand what the patient is saying. He understands more quickly the rôle the patient places him in, and recognizes more readily how his behavior—concerned, interested listening—is therapeutic for the patient. In this process the resident becomes more content with the kind of help he is able to give to the patient, and the patient seems to get along better and is able to do more for himself outside of the doctor's office, and seems to need less intensive contact with the physician.

Summary

In this paper I have attempted to illustrate the rôle of the psychosomatic seminar in helping the physician understand the usually difficult doctor-psychosomatic patient relationship. The opportunity for continuous consultation and weekly discussion of cases permits the physician to understand the rôles the patient places him in, and his own human reactions to the patient, and thus helps him work more effectively with the patient, with less wear and tear on himself.

The use of such continuous seminars by physicians in private practice may be one method of helping them treat more effectively a larger number of severely disturbed psychosomatic patients.

Summario in Interlingua

Disordines psychosomatic reflecte usualmente sever subjacente problemas personal del patiente in question. Le medico qui labora con tal patientes incontra frequentemente numerose problemas in le relation inter patientes e medico que reduce le efficacia del tractamento.

In un colloquio clinico-psychosomatic, le membros del personal interne de un hospital universitari ha le opportunitate de orientar lor manipulation de patientes psychosomatic sub le influentia de consultationes septimanal con le medico-in-chef del clinica e un psychiatro. Il pare que tal consultationes adjuta le interno a acceptar le necessitate de laborar dedicatemente con le patiente qui es invalidate per innumerabile gravamines somatic. Le interno apprende a visar in tal casos a restablir le functionamento del patiente per medio del mantenentia de un "compensation psychologic," exactemente como ille visarea a adjutar un patiente cardiac per establir un compensation physiologic. Ille apprende a ascoltar, a utilisar le medio de attentive sympathia pro adjutar le patiente con "psychoticoide" symptomas somatic qui nonobstante non acceptarea le recommendation de un transferimento al clinica de psychiatria. Le interno etiam apprende que in le caso de patientes con classic

symptomas psychosomatic, i.e. con asthma, ulcere peptic, obesitate, etc., le interpretationes offerite per le manuales scholastic es apparentemente de pauc adjuta e pote, de facto, disrumper su effortios. Assi ille comencia gradualmente a comprender que un indispensabile agente therapeutic in su labor con le patiente es le relation inter medico e patiente. Ille comencia recognoscer que le hostilitate del patiente o su attachamento, su exigentia, sexualitate, amor, etc. es concentrate super ille proque pro le patiente ille ha devenite al tempore presente un representante de un persona importante ex le passato del patiente.

Le opportunitates de apprender a comprender in le curso del colloquio le relation inter medico e patiente, de specular in re le possibile formas de reaction del parte del patiente verso le medico e del parte del medico verso le patiente, de apprender a previder iste reactiones, etc., es certo de grande valor practic. Le consulentes describe super le base de lor plus extense experientias lor proprie emotiones in lor contactos con le patientes e assiste le internos a reguardar non solmente le patientes sed etiam se mesme como creaturas human con inevitabile maculas e debilitates in lor personalitate. Si le membros del personal apprende assi que lor reactiones verso le patientes es natural e require de lor parte nulle attitude defensive, illes deveni plus relaxate in lor contactos con lor patientes; illes deveni plus attentive; illes senti minus fortemente le tendentia a fortiar le collaboration del patientes pro satisfacer lor fame de successo; e in summa illes deveni de assistentia plus benefic al severmente disturbate patientes psychosomatic.

Il pare possibile que tal colloquios psychosomatic esserea etiam de valor pro medicos independente qui labora in lor practica private con difficile patientes psychosomatic.

CASE REPORTS

THE LUTEMBACHER SYNDROME: A PHYSIOLOGIC STUDY AND CASE REPORT *

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The association of mitral stenosis with an interatrial septal defect was noted by Lutembacher in 1916,[1] and his name has since been applied to this combination of lesions. In 1933 McGinn and White [2] collected 23 cases and added another of their own. In 1934 Roesler [3] found associated lesions of the mitral valve in 30 of the 62 instances of the interatrial defects which he reviewed. Burrett and White [4] later reported that, of the combined series of Roesler and those gathered since then, 53.8% of the cases of interatrial defects had associated mitral stenosis.

However, Nadas and Alimurung [5] have stressed the comparative infrequency of mitral stenosis with interatrial septal defects. This has become of practical importance with the development of definitive cardiac surgery for both mitral stenosis and interatrial septal defects. It has now become increasingly apparent that proved instances of Lutembacher's syndrome are comparatively infrequent.

The following case is therefore reported as an instance of marked mitral stenosis with an interatrial defect and tricuspid insufficiency which was studied by cardiac catheterization and later came to postmortem examination.

Case Report

First Admission: A 32 year old woman was first admitted to the University Hospital on January 22, 1952, complaining of shortness of breath for six years.

As a child she had participated in active sports without any difficulty. Six years previously she first noted shortness of breath. Within two weeks of its appearance it had become noticeably worse. She was then told for the first time that she had rheumatic heart disease and was digitalized, with subsequent improvement in her ability to carry on her activities. Three years before admission, after a prolonged period of tachycardia, she was kept in bed for seven weeks and digitalis was resumed and continued until the time of admission. She continued to have numerous episodes of tachycardia, occasionally associated with fever and upper respiratory infections. The shortness of breath gradually increased so that she had to be carried up stairs by her husband. She had no orthopnea or ankle edema. There was no history of scarlet fever, rheumatic fever or chorea. Prior hospitalizations had been for an appendectomy and two uneventful deliveries 14 and 11 years previously. At the time of the appendectomy at another hospital, 10 years previously, no murmurs were described. Her family history and system review were noncontributory.

* Received for publication November 16, 1954.
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Physical examination revealed a well developed, well nourished white woman in no acute distress. The blood pressure was 110/70 mm. Hg; respirations, 20/min.; the pulse rate was 90/min. and regular. There was no cyanosis or edema. The lungs were clear on percussion and auscultation. The heart was enlarged to the anterior axillary line on the left and 4 cm. to the right of the sternum in the fourth interspace. A diffuse fine systolic thrill was palpable to the left of the sternum in the second to fourth interspaces. A mid-diastolic thrill was palpable 2 cm. medial to the apex. The second heart sound in the pulmonic area was accentuated. A harsh systolic murmur, grade 3 in intensity, was heard over the entire precordium and was loudest at the site of the systolic thrill. A mid-diastolic rumble was heard at the mitral area, synchronous with the diastolic thrill. There was a short presystolic rumble at the mitral area, ending with a loud first heart sound. The liver edge was palpable 1 to 2 cm. below the right costal margin.

Roentgen examination of the chest revealed marked generalized enlargement of the heart, especially of the pulmonary artery segment, right ventricle and left ventricle. On fluoroscopic examination the pulmonary artery and its branches were seen to pulsate vigorously but there was no hilar dance. There was a moderate degree of pulmonary congestion bilaterally. The transverse measurement of the chest was 27.6 cm. The maximal enlargement to the left was 13.3 cm.; to the right, 5.5 cm. The electrocardiogram was characteristic of right ventricular hypertrophy; the PR interval was 0.20 second, and the rate was 88. Regular sinus rhythm was present. The venous pressure was 78 mm. of saline. The arm-to-tongue circulation time was 39 seconds (Decholin), while the arm-to-lung time was 10 seconds (ether) with no peripheral tingling.

Laboratory findings were: hemoglobin, 15.6 gm./100 ml.; hematocrit, 47%; white blood count, 8,650/cu. mm., with a normal differential; corrected sedimentation rate, 13 mm./hour (Wintrobe) and later 9, and 6. Routine blood chemistry studies were normal.

She was maintained on 0.2 mg. of digitoxin daily, low salt diet and ammonium chloride, and was discharged somewhat improved on February 15, 1952.

Second Admission: The patient was re-admitted on April 14, 1952, because of palpitation and a rapid heart rate for one day. During the preceding two months there had been frequent episodes of sudden, rapid heart action despite quinidine medication.

On admission she was able to lie comfortably in bed without any respiratory distress. The pulse rate was 134/minute and regular. The blood pressure was 105/60 mm. Hg. No significant changes were found on examination of the heart. The lungs were normal on auscultation and percussion. The liver was palpable 3 cm. below the right costal margin and was moderately tender.

The electrocardiogram was similar to that recorded on the previous admission except for the presence of atrial flutter with a 2:1 atrial ventricular response. With Digoxin and quinidine therapy, regular sinus rhythm was restored after a transient period of atrial fibrillation. She remained afebrile and was discharged on April 30.

Third Admission: On September 27, 1953, this patient was admitted for the third time. During the one and a half years since her previous admission she had continued to have occasional episodes of palpitation and rapid heart action. She was maintained on Digoxin, 0.25 mg. three times daily, and had taken quinidine sulfate irregularly. The shortness of breath had become worse, and she was able to perform only the lightest household chores.

There was no edema or cyanosis. She was able to lie flat without any respiratory distress. The blood pressure was 130/75 mm. Hg; pulse rate, 64/minute and grossly irregular in rate, rhythm and force. Examination of the neck revealed a systolic pulsation of the jugular veins. The size of the heart was the same on

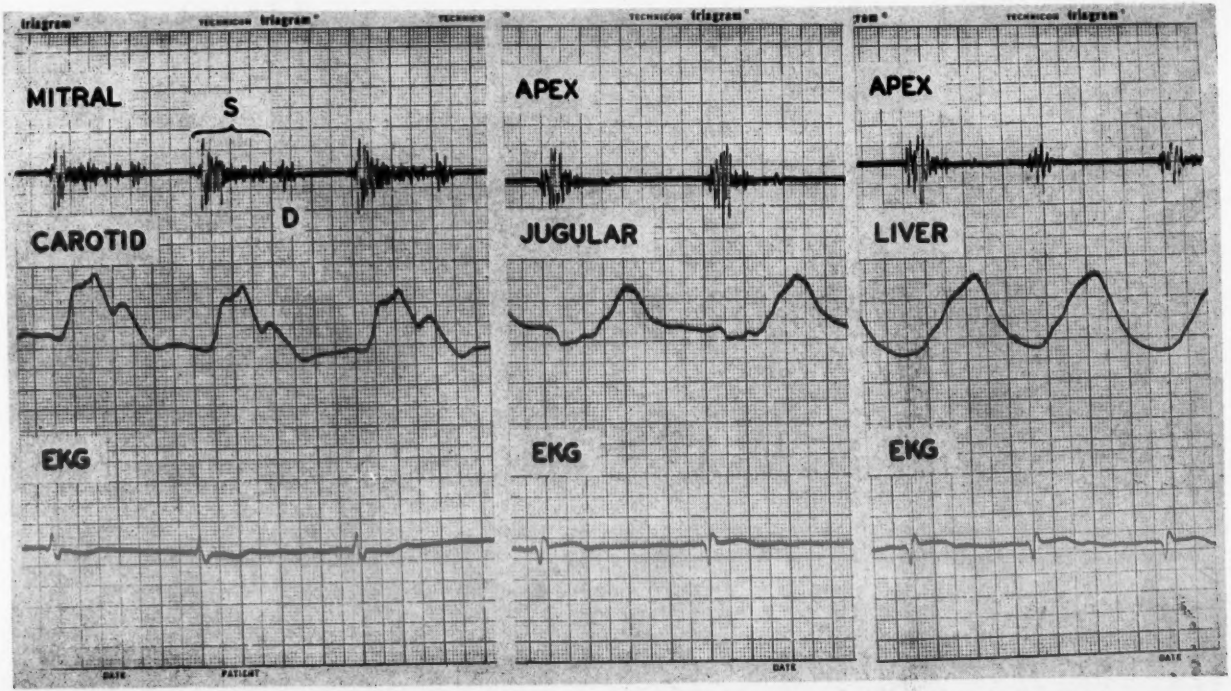

FIG. 1. Stethogram, pulse and liver tracings. At the mitral area is recorded a systolic murmur (S) followed by a mid-diastolic murmur (D). There is a positive jugular and liver pulse wave, with the rise occurring in ventricular systole. (See text for details.)

percussion as on the previous admissions. A diffuse fine systolic thrill was palpable to the left of the sternum in the second to fourth interspaces. A thrill was palpable in mid-diastole in the mitral area. The second sound in the pulmonic area was accentuated. A rough grade 3 systolic murmur was heard over the entire precordium and was loudest at the site of the systolic thrill and at the apex. A mid-diastolic rumble was heard at the mitral area, synchronous with the diastolic thrill. The liver was palpable 1 to 2 cm. below the right costal margin on inspiration, and there was a systolic pulsation of the liver apparently synchronous with that in the jugular vein. Tracings were obtained of the heart sounds, liver pulsations and jugular pulsations.[6]

The first sound at the mitral area was of high amplitude and was followed by a systolic murmur of high frequency and moderate amplitude (figure 1). The second sound was synchronous with the dicrotic notch of the carotid pulse and was followed by a short quiet interval. There was then a series of vibrations of relatively low frequency and moderate amplitude.

Both the jugular and liver pulse tracings were characterized by positive waves, with the rise occurring in ventricular systole (figure 1). The positive wave began in early or mid-systole, with the peak reached near the time of the second sound on the liver tracing and slightly later in the jugular tracing. The jugular tracing was also characterized by an additional small positive wave on the upstroke of the larger positive wave.

TABLE 1

Cardiac Catheterization

Site	Oxygen (Vol. %)	Pressure (mm. Hg)
Superior vena cava	9.8	
Right atrium (high)	13.3	
Right atrium (mid)	15.6	12/4
Right atrium (tricuspid)	17.6	
Right ventricle	17.2	45–50/4
Main pulmonary artery	17.6	35–40/12–16
Right pulmonary artery	17.7	
Right femoral artery	18.3 (92% saturation)	
Oxygen capacity	20.1	

Laboratory findings were: hemoglobin, 13.8 gm./100 ml.; hematocrit, 46%; corrected sedimentation rate 6 mm./hour (Wintrobe). Routine blood chemistries and electrolytes were normal.

The venous pressure was 43 mm. of saline. The arm-to-lung circulation time was 16 seconds (ether) and the arm-to-tongue time was 22 seconds (Decholin). An electrocardiogram on admission revealed atrial fibrillation and was otherwise similar to that of the previous admissions (figure 2). A roentgen examination of the chest revealed a transverse heart diameter of 17.9 cm. and a transverse chest diameter of 27.0 cm. (figures 3, 4).

Following admission the patient was continued on 0.25 mg. Digoxin three times daily and 400,000 units penicillin twice daily. On September 30 cardiac catheterization was performed (table 1). This procedure was carried out with the catheter inserted into a left antecubital vein.[7, 8] There was an increase of 3.5 vol.% oxygen between the oxygen content of the specimen obtained from the superior vena cava and that obtained from the high right atrium. There was an additional increment of 4.3 vol.% between the latter specimen and that obtained from the right atrium near the tricuspid valve. The oxygen saturation of the right femoral artery specimen was 92%.

The right atrial pressure was elevated and there was a definite elevation in the right ventricular systolic pressure to 45 to 50 mm. Hg. The systolic pressure in the right ventricle exceeded that of the pulmonary artery by about 10 mm. Hg. The

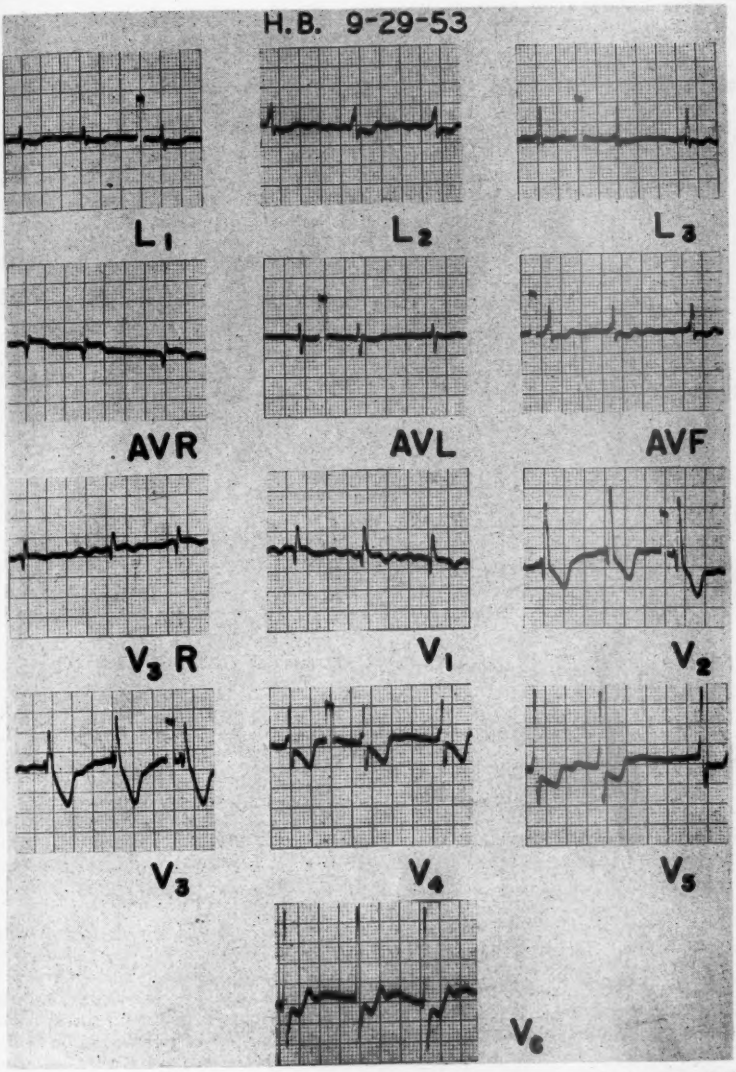

FIG. 2. Electrocardiogram. Atrial fibrillation with an average ventricular rate of 80 per minute. There is a prominent R' in V_3R to V_3, and a prominent S wave in V_4 to V_6. The ST segment sags and T is diphasic in Leads I, II and aVF. ST is depressed and T inverted in V_2 to V_4. ST is depressed and T diphasic in V_5 to V_6. This tracing indicates right ventricular hypertrophy. Digitalis plays a role in producing the ST and T changes.

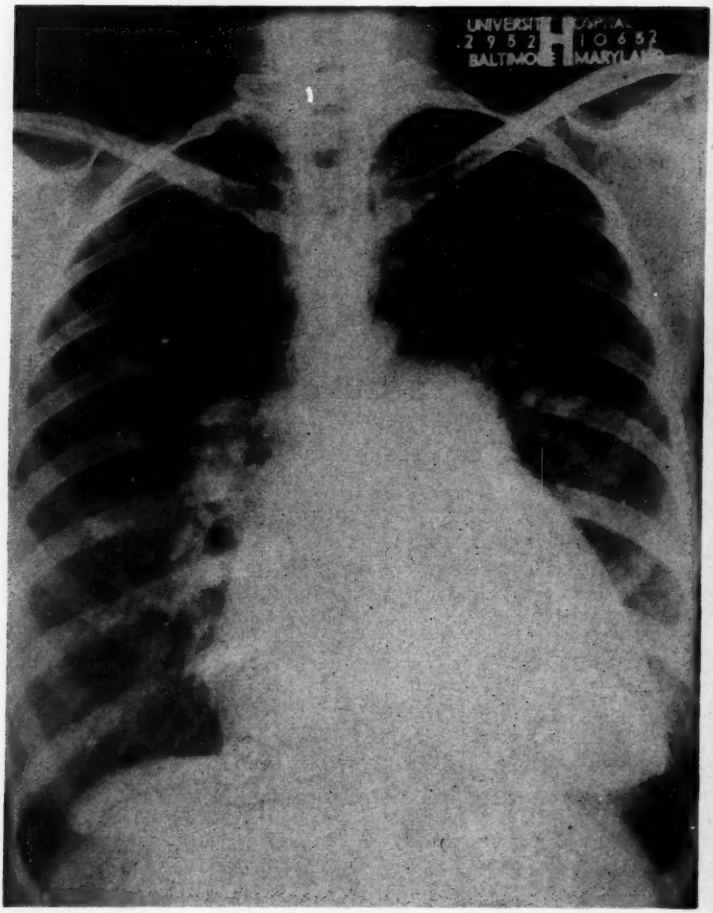

FIG. 3. Roentgenogram. The heart is enlarged to the right and left. The pulmonary artery segment is extremely prominent.

contour of the right atrial tracing revealed a positive wave beginning in early ventricular systole, and reaching its greatest height appreciably later than the peak of ventricular systole. On the upstroke there was a smaller positive wave (figure 5).

The right ventricular pulse curve revealed a diastolic dip reaching its nadir somewhat later than the systolic peak in the right atrial pulse.

The patient remained hospitalized until October 27, 1953, at which time a thoracotomy was performed. The mitral valve was found to be markedly stenosed, the orifice being a slit 1 cm. in length and about 2 mm. wide. No regurgitant stream was felt. The surgeon described an interatrial septal defect 2 cm. in diameter. A

mitral commissurotomy was performed, the tear being made along the septal commissure. After the commissurotomy there was no regurgitation, and the chest was closed in the routine manner with underwater thoracotomy drainage.

The patient was returned to the ward in good condition. Her blood pressure was then 110/80 mm. Hg and her pulse 100/min. Three hours postoperatively, however, bloody fluid began to appear in the thoracotomy drainage tube and within a period of three and a half hours approximately 2,700 c.c. of blood were lost. Four pints of whole citrated blood were given slowly and the blood pressure remained approximately 60/0 mm. Hg. An additional 3,500 c.c. of whole citrated blood were

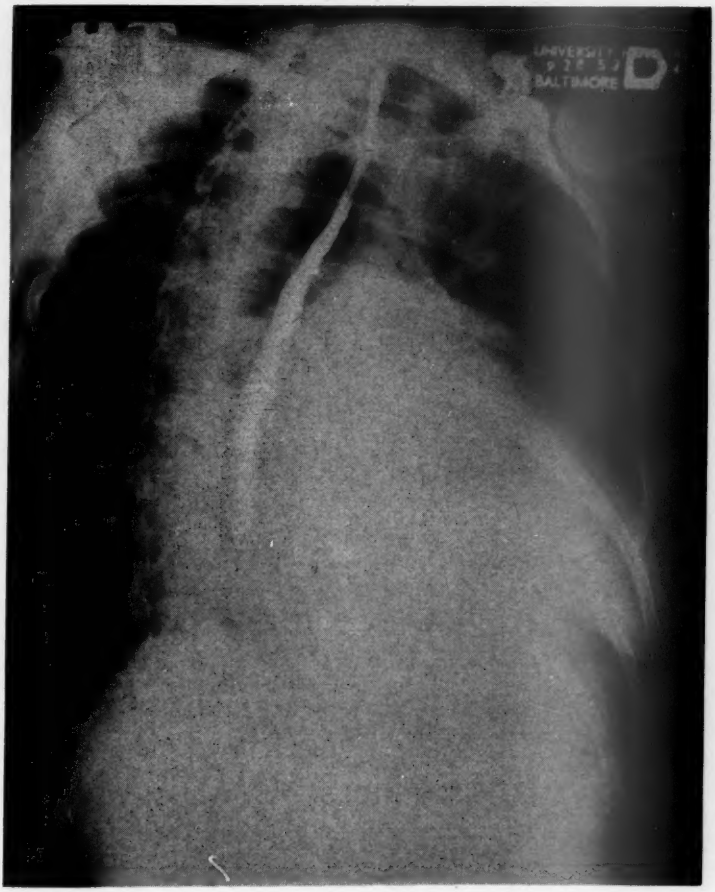

FIG. 4. Roentgenogram (right anterior oblique). The heart is enlarged anteriorly and posteriorly, with deviation of the barium filled esophagus posteriorly. The pulmonary artery segment is prominent.

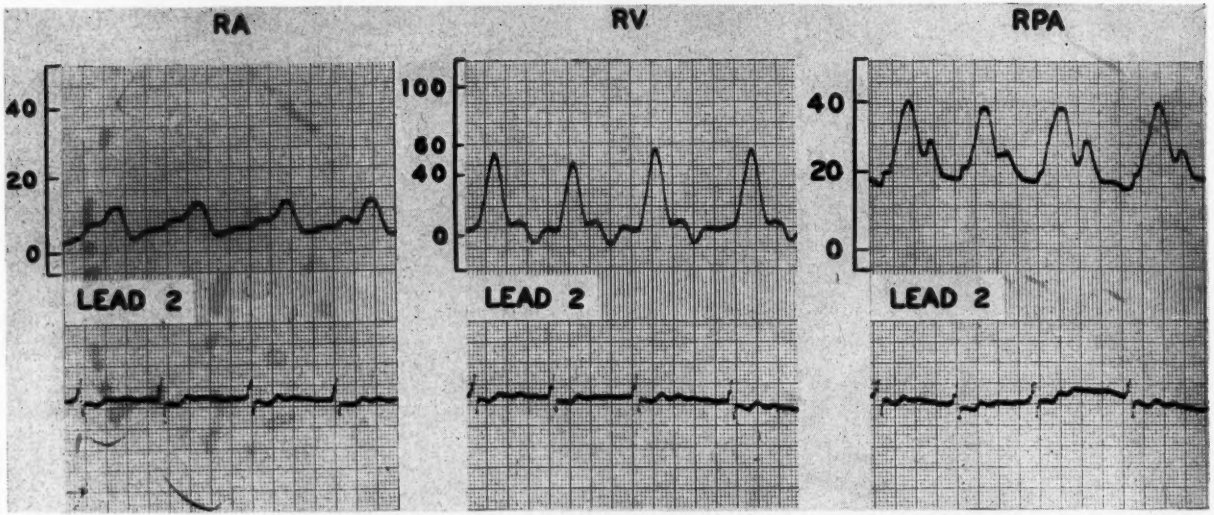

FIG. 5. Right atrial (RA), right ventricular (RV) and right pulmonary artery (RPA) pulse tracings recorded in mm. of Hg. Note the double positive wave occurring early in ventricular systole in the right atrial tracing. There is a negative dip in the right ventricular tracing. (See text for details.)

given with 45 mg. of Wyamine. The blood pressure slowly increased to 80/0 mm. Hg. Pulmonary edema occurred and cleared following the use of Cedilanid and positive pressure oxygen. On the following day her temperature rose to 106° F. rectally but fell to 102° F. with sponging. Her sclerae were then noted to be icteric. The hemoglobin at this time was 16.8 gm./100 ml.; hematocrit, 46%; CO_2 content, 20 mEq./L.; chlorides, 110 mEq./L. On the next day her respirations became more labored and increased to 50/min. She became weaker and died on the second postoperative day (October 29, 1953). Shortly before death the laboratory findings revealed: CO_2 content, 23 mEq./L.; chlorides, 89 mEq./L.; sodium, 118 mEq./L.;

FIG. 6. The heart as seen from the left side of the interatrial septum. Note the defect in the septum. Below the defect can be seen the deformed, stenotic mitral valve as viewed from above.

potassium, 7 mEq./L.; van den Bergh reaction, 3.8 mg./100 ml. direct and 1.8 mg./100 ml. indirect. An autopsy was performed.

AUTOPSY

The operative incision was opened and inspected for possible sources of bleeding. None was found.

Heart: The heart weighed 550 gm. The myocardium was flabby but of uniform consistency. The pericardial cavity contained fibrinous exudate. The distal part of the left auricle had been amputated, and a purse-string suture was present in the remaining portion. This was properly tied, but when the left auricle was compressed

blood was seen to appear through one of the suture holes. This was of questionable significance. Small blood clots were recovered from this area. Areas of fibrous thickening of the epicardium were noted, particularly over the auricles. Subepicardial "milk patches" were seen near the apex on the right and left ventricle. The coronary arteries were patent throughout and showed no atherosclerosis. The auricular endocardium, particularly on the left side, showed dense white thickening. The interatrial septum was extremely thin and almost transparent, except for a circumferential rim of 2 to 3 mm. which contained muscle tissue. There was an oval defect in the superior anterior portion 2 cm. in its largest diameter (figure 6). Its edges were

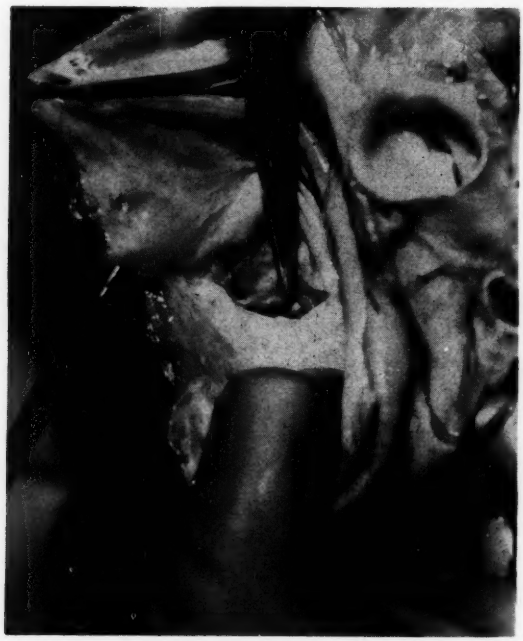

FIG. 7. The heart as seen from above the mitral valve. To the right of the instrument is the tear at the front of the original inner commissure. The stenotic deformed mitral valve orifice lies to the left.

scarred and thickened, particularly along the superior margin, where there was partial calcification. The mitral valve showed marked stenosis, and the original valve orifice was seen to have been slitlike and about 1 cm. in length (figure 7). A tear was present in the valve at the point of the original inner commissure. The fused margins of the anterior cusp of the mitral valve extended in a triangular sheetlike mass to insert directly into the scarred papillary muscles, with small ridges representing the fused chordae tendineae. A similar deformity of the posterior cusp was present. The cusps of the aortic valve showed marked thickening, in areas measuring 3 mm. in their midportion, and minimal fusion of their commissures. On the endocardium just below the anterior aortic sinus was an irregular dense white area of scarring

which measured roughly 2 by 1 cm. The tricuspid valve was thickened and presented an almost straight free margin, due to scarring, with a few small fenestrations persisting near the free margin. The chordae tendineae were short and thickened. The papillary muscles were hypertrophied. The pulmonary artery was dilated. The mitral valve ring measured 7.5 cm. in circumference, the aortic 5.5 cm., tricuspid 14 cm., and the pulmonic 8 cm. The left ventricle averaged 1.7 cm. in thickness, the right, .5 cm.

Lungs: Two to three small hemorrhagic infarcts measuring about 2 cm. in diameter were noted in the periphery of each lung.

Liver: The surfaces of the liver were very granular. The liver showed marked accentuation of the lobular architecture. It weighed 1,500 gm.

Microscopic Notes: Heart: The myocardial fibers showed evidence of hypertrophy and mild interstitial fibrosis. Liver: There was marked congestion accompanied by central necrosis and hemorrhages.

Discussion

In normal sinus rhythm the normal jugular pulse reveals a positive wave (a wave) due to atrial systole. Following this there may be a small positive wave (c wave) due to elevation and closure of the tricuspid valve at onset of ventricular systole.[9] There is then a negative wave which is apparently due to atrial diastole and the descent of the base of the heart. A later positive wave (v wave) then appears which is due to the passive filling of the atrium. The crest of this wave is coincident with the opening of the tricuspid valve. In atrial fibrillation, the "a" wave due to atrial contraction is no longer seen.

The jugular tracing of this patient demonstrated a prominent positive wave beginning in the middle of ventricular systole and reaching its peak after the second sound. The normal systolic dip was modified and replaced by a later positive wave merging with a prominent V wave. MacKenzie [10] referred to this form of jugular wave as the ventricular type of venous pulse. Wiggers [11] and others have also described this phenomenon. The diastolic murmur recorded at the mitral area began at the crest of the positive wave in the jugular pulse. The crest marks the opening of the tricuspid and mitral valves.

The contour of the right atrial pressure tracing was characterized by a positive systolic wave on the upstroke of which was an additional positive wave. Absent from the atrial tracing was the normal negative wave during ventricular systole. The positive wave apparently represented insufficiency of the tricuspid valve. As the right ventricle contracts blood enters the right atrium, producing the positive wave. Occasionally the small dip on the upstroke may represent partial closure of the tricuspid valve.[12] The positive deflection due to regurgitation may merge with the normal V wave in instances of marked tricuspid insufficiency to produce a single positive systolic wave. This regurgitant wave is transmitted retrograde to the inferior vena cava and superior vena cava as a positive systolic pulsation of the jugular vein and liver. There may be differences in timing due to the different distances that the pulsations have to traverse and to the recording devices employed. The crest of the liver pulse tracing is almost synchronous with the large positive wave recorded in the right atrium.

The pressure curve obtained in the right ventricle revealed a negative wave in early diastole. Early diastolic dips have been observed in patients with right

ventricular failure, myocardial fibrosis and constrictive pericarditis.[13-18] McChord and Blount [19] and Bloomfield and associates [13] have also reported an early diastolic dip in tricuspid insufficiency. The mechanism of the diastolic dip in constrictive pericarditis is ascribed to impaired diastolic filling of the right ventricle.

All of these findings supported the initial clinical impression of tricuspid insufficiency. However, it is difficult to determine whether tricuspid insufficiency is due to an organic valvular lesion or is secondary to right ventricular failure alone. MacKenzie [10] repeatedly stressed the natural tendency to tricuspid incompetency and deplored how frequently it was missed. Müller and Shillingford [12] have described 21 patients with tricuspid insufficiency and discussed the difficulty in distinguishing organic lesions from functional tricuspid insufficiency. Recently, increasing instances of tricuspid insufficiency have been noted among patients with mitral stenosis.[20]

In addition to mitral stenosis, the heart described in the present report also demonstrated involvement of the aortic valve. There were also the thickening and scarring of the tricuspid valve and of the chordae tendineae. While this alone may have been of questionable significance, the combination with an enlarged right ventricle and dilated ring probably increased the degree of tricuspid regurgitation. As Friedberg [9] states, "Tricuspid insufficiency is enhanced when dilatation of the right ventricle is associated with concomitant dilatation of the tricuspid ring."

The difference between the systolic pressures recorded in the right ventricle and in the pulmonary artery is of interest. It is compatible with a mild degree of pulmonic stenosis and may be due to the drop in pressure often found as blood enters a markedly dilated pulmonary artery. At autopsy no definite evidence of pulmonic stenosis could be demonstrated. A difference in pressures was recently reported preoperatively in a patient with an interatrial septal defect.[21] The difference was ascribed to functional pulmonic stenosis reflecting a greatly elevated pulmonary artery blood flow rather than anatomic stenosis. It was detected before the interatrial defect was repaired and disappeared postoperatively.

It is relevant to note that Bedford and associates [22] stated that the ". . . systolic thrill and murmur so often audible over the pulmonary area can be readily explained by the dilatation of both conus and pulmonary artery giving rise to a relative stenosis of the lesser distended pulmonary ring."

The catheterization results were indicative of a left-to-right shunt entering the right atrium.[23-25] This is usually due to an interatrial septal defect, although an anomalous pulmonary vein may present similar findings.[23, 26]

At the present time, when mitral commissurotomies are so frequently performed and interatrial defects successfully repaired,[21, 27-29] the diagnosis of Lutembacher's syndrome is more than an academic problem. It is not sufficient to assume that the only criterion necessary for the diagnosis of a mitral stenosis accompanying a demonstrable septal defect is the presence of a diastolic murmur at the apex. Nadas and Alimurung [5] state that an apical diastolic murmur is rather common in congenital heart disease in the absence of mitral stenosis. This may be due to a functionally stenotic valve. In interatrial septal defects it may be due to relative tricuspid stenosis, or actually originate at the site of the

atrial defect at the time of the maximal shunt through the defect, that is, in mid-diastole or presystole.[5, 30] Recently Blount and his associates [21] reported on the successful closure of five interatrial septal defects. Of these patients, three had medium-pitched, short mid-diastolic murmurs along the lower left sternal border. This murmur, which was attributed to functional tricuspid stenosis, disappeared postoperatively in all three patients. They believe that Lutembacher's syndrome is diagnosed much more frequently than is justified by its rare occurrence.

There is justifiable disagreement as to the true incidence of mitral stenosis and interatrial septal defects. In 1933 McGinn and White [2] reviewed the literature, added another case, and reported 24 patients with the associated lesions. In 1934 Roesler [3] reviewed the subject of interatrial septal defects and found lesions of the mitral valve in 30 of the 62 cases which he had collected. Of these, six presented the buttonhole type. It is relevant to note that a definite venous pulse in the veins of the neck and/or of the liver was described in 12 cases, in four of whom he could find no mention of an organic valvular lesion. Burrett and White [4] in 1945 added an additional 31 cases to Roesler's series, for a total of 93. Of these, 53.8% had associated mitral stenosis.

Burrett and White [4] point out that the associated lesion is frequently missed, since it was recognized clinically in only nine of the 19 cases among the 31 autopsies which they reported. Similarly, Brown [31] states that mitral stenosis should be suspected in every case of interatrial septal defect. However, Nadas and Alimurung [5] point out that only six of the 62 cases of Roesler's series really had "buttonhole stenosis" while the rest ranged from mitral insufficiency to "thickening of the mitral valve." They further reported 25,000 consecutive autopsies in which there were 87 instances of interatrial septal defects and five mitral stenosis. Even when they excluded a large number which were infants, only 10% of the interatrial defects presented the combined lesions. They quote a personal communication from J. E. Edwards that at the Mayo Clinic the autopsy material contains 26 examples of interatrial defects and only one case of Lutembacher's syndrome.

Cardiac surgery now furnishes additional information on the relative infrequency of the associated lesions. Bailey and his associates [27] found two associated instances of mitral stenosis among the 21 patients operated upon for closure of interatrial septal defects. They found that the coexistence of mitral stenosis in patients with interatrial septal defects proved no serious obstacle to successful simultaneous surgical correction of both conditions. Kay [29] found two instances of the associated lesions among the eight patients in whom he closed an interatrial defect. The technic employed was similar, i.e., the mitral commissurotomy was performed with the finger inserted through the right auricle and septal defect.

There are several types of defects of the atrial septum. These are: an absent or rudimentary septum, persistent ostium primum, persistent ostium secundum, and a patent foramen ovale. A persistent ostium primum is characterized by a large gap at the base of the interatrial septum. A persistent ostium secundum is a gap in the upper and posterior part of the septum, above the fossa ovalis. There may be valvular or slitlike patency of the foramen ovale in 20 to 30% of the cases. This is usually of no clinical importance unless the pressure increases in the right atrium so that the potential patency becomes manifest. At

times there may be some question as to whether an interatrial defect is a persistent ostium secundum or widely patent foramen ovale. However, as Brown [31] states in discussing persistent ostium secundum, ". . . the valve membrane and the limbus of the fossa ovalis are absent in a true defect of this category. The term 'widely patent foramen ovale' should be applied only to a distention of a functionally patent foramen ovale, without congenital septal defect." Taussig [32] similarly states: "The term patent foramen ovale should be restricted to those cases in which the foramen ovale is normally formed and is covered by a valve which is not completely sealed."

In the case here reported there was an oval defect 2 cm. in its longest diameter and well above the atrioventricular margin. In the absence of any vestige of a valve membrane or limbus of a fossa ovalis, it is apparently an ostium secundum.

The case reported by Lutembacher in 1916 [1] was that of mitral stenosis and congenital malformation of the septum primum. The remaining part of the septum was nearly entirely membranous, transparent, very thin, and like a normal mitral valve. In addition, he noted that the tricuspid valve was very dilated, and discussed the possibility of reflux into the venae cavae when the right side of the heart became insufficient. It has been variously postulated that mitral stenosis may cause a patent foramen ovale to become an actual atrial defect as the pressure in the left atrium increases. Taussig believes that the existence of an interatrial communication predisposes to the development of rheumatic infection and hence of rheumatic mitral stenosis.[32] Lutembacher [1, 33] stated that mitral stenosis could be congenital in origin and prevent the closure of the interatrial septum.

It is being increasingly felt that the mitral stenosis in Lutembacher's syndrome is on an acquired basis. Ferencz and associates [34] recently reported nine new cases of congenital mitral stenosis and reviewed 34 gathered from the literature since 1846. They state that they ". . . have not yet discovered a case of mitral stenosis, undeniably of congenital origin, associated with a significant defect of the interatrial septum." However, Schopf [35] has reported an instance of Lutembacher's syndrome in a two day old child in whom there was congenital mitral stenosis and wide patency of the foramen ovale.

There was involvement of the mitral, aortic and tricuspid valves in the patient here reported. The multiple valvular lesions were indicative of inflammatory disease, probably on a rheumatic basis. This patient is therefore reported as an instance of combined congenital interatrial defect and acquired mitral stenosis.

Summary

1. A case of combined congenital interatrial defect and acquired mitral stenosis is presented who was catheterized, operated upon and later came to autopsy.

2. The presence of tricuspid insufficiency as a complicating lesion was demonstrated and is discussed.

3. Lutembacher's syndrome occurs much more infrequently than it is diagnosed or suspected prior to anatomic demonstration.

4. The disagreement as to the frequency of Lutembacher's syndrome diagnosed clinically and later established at autopsy is discussed.

Summario in Interlingua

Es presentate un caso de congenite defecto interatrial combinate con acquirite stenosis mitral.

Catheterisation cardiac demonstrava derivation sinistro-dextere a in le atrio dextere. Registrationes del pulsos jugular e hepatic esseva executate, e un defecto del septo interatrial esseva discoperite. Le patiente moriva le secunde die post le operation. Le constationes includeva un defecto interatrial con un diametro maximal de 2 cm, marcate stenosis mitral, e affection del valvulas tricuspide e aortic. Le constatationes physiologic es discutite. Le pertinente litteratura es revidite.

Le diagnose clinic de syndrome de Lutembacher es plus frequente que le demonstration del combination de lesiones per subsequente examines. Murmures diastolic apical in le presentia de congenite morbo cardiac non es infrequente. Il es un exception plus tosto que le regula que in tal casos il ha formas significative de stenosis mitral. Es discutite le disparitate inter le frequentia del diagnose clinic de syndrome de Lutembacher e le frequentia de su description al tempore del autopsia.

BIBLIOGRAPHY

1. Lutembacher, R.: De la sténose mitrale avec communication interauriculaire, Arch. d. mal. du cœur **9**: 237, 1916.
2. McGinn, S., and White, P. D.: Interauricular septal defect associated with mitral stenosis, Am. Heart J. **9**: 1, 1933.
3. Roesler, H.: Interatrial septal defect, Arch. Int. Med. **54**: 339, 1934.
4. Burrett, J. B., and White, P. D.: Large interauricular septal defect with particular reference to diagnosis and longevity, Am. J. M. Sc. **209**: 355, 1945.
5. Nadas, A. S., and Alimurung, M. M.: Apical diastolic murmurs in congenital heart disease, Am. Heart J. **43**: 691, 1952.
6. Grishman, A., Kroop, I. G., Steinberg, M. F., and Dack, S.: Presystolic pulsations of the liver in the absence of tricuspid disease, Am. Heart J. **40**: 731, 1950.
7. Cournand, A., Lauson, H. D., Bloomfield, R. A., Breed, E. S., and Baldwin, E. de F.: Recording of right heart pressures in man, Proc. Soc. Exper. Biol. and Med. **55**: 34, 1944.
8. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Seibel, R. E., and Evans, J. M.: Studies of congenital heart disease. I. Technique of venous catheterization as a diagnostic procedure, J. Clin. Investigation **26**: 547, 1947.
9. Friedberg, C. K.: Diseases of the heart, 1949, W. B. Saunders Co., Philadelphia.
10. MacKenzie, J.: The interpretation of the pulsations in the jugular veins, Am. J. M. Sc. **134**: 12, 1907.
11. Wiggers, C. J.: Circulation in health and disease, 1923, Lea and Febiger, Philadelphia.
12. Müller, O., and Shillingford, J.: Tricuspid incompetence, Brit. Heart J. **16**: 195, 1954.
13. Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W.: Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardio-circulatory disease, J. Clin. Investigation **25**: 639, 1946.
14. Hansen, A. T., Eskildsen, P., and Gotzsche, H.: Pressure curves from the right auricle and the right ventricle in chronic constrictive pericarditis, Circulation **3**: 881, 1951.
15. McKusick, V. A.: Chronic constrictive pericarditis. II. Electrokymographic studies and correlations with roentgenkymography, phonocardiography, and right ventricular pressure curves, Bull. Johns Hopkins Hosp. **90**: 27, 1952.

16. Yu, P. N. G., Lovejoy, F. W., Joos, H. A., Nye, R. E., and Mahoney, E. B.: Right auricular and ventricular pressure patterns in constrictive pericarditis, Circulation **7**: 102, 1953.

17. Harvey, R. M., Ferrer, M. I., Cathcart, R. T., Richards, D. W., and Cournand, A.: Mechanical and myocardial factors in chronic constrictive pericarditis, Circulation **8**: 695, 1953.

18. Wilson, R. H., Borden, C. W., Hoseth, W., Sadoff, C. N., and Dempsey, M. E.: The pathologic physiology and diagnostic significance of pressure pulses in the right heart in patients with chronic constrictive pericarditis and pericardial effusion, Clin. Res. Proc. **2**: 9, 1954.

19. McChord, M. C., and Blount, S. G.: The hemodynamic pattern in tricuspid valve disease, Am. Heart J. **44**: 671, 1952.

20. Lukas, D. S., and Sepulveda, G.: Diagnosis of tricuspid insufficiency: clinical features in 60 cases with associated mitral valve disease, Clin. Res. Proc. **2**: 63, 1954.

21. Blount, S. G., Swan, H., Gensini, G., and McChord, M. C.: Atrial septal defect. Clinical and physiologic response to complete closure in five patients, Circulation **9**: 801, 1954.

22. Bedford, D. E., Papp, C., and Parkinson, J.: Atrial septal defect, Brit. Heart J. **3**: 37, 1941.

23. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Sosman, M. C., and Evans, J. M.: Studies of congenital heart disease. III. Venous catheterization as a diagnostic aid in patent ductus arteriosus, tetralogy of Fallot, ventricular septal defect, and auricular septal defect, J. Clin. Investigation **26**: 561, 1947.

24. Brannon, E. S., Weens, H. S., and Warren, J. V.: Atrial septal defect. Study of hemodynamics by the technique of right heart catheterization, Am. J. M. Sc. **210**: 480, 1945.

25. Cosby, R. S., and Griffith, G. C.: Interatrial septal defect, Am. Heart J. **38**: 80, 1949.

26. Cosby, R. S., Griffith, G. C., Zinn, W. J., Levinson, D. C., Dimitroff, S. P., Oblath, R. W., and Jacobson, G.: Cardiac catheterization in interatrial septal defect, Am. J. Med. **14**: 4, 1953.

27. Bailey, C. P., Bolton, H. E., Jamison, W. L., and Neptune, W. B.: Atrio-septopexy for interatrial septal defects, J. Thoracic Surg. **26**: 184, 1953.

28. Gross, R. E., Watkins, E., Pomeranz, A. A., and Goldsmith, E. I.: A method for surgical closure of interauricular septal defects, Surg., Gynec. and Obst. **96**: 1, 1953.

29. Kay, E. B.: Discussion of Shumacker, H. B., Moore, T. C., and King, H.: The experimental closure of atrial septal defects, J. Thoracic Surg. **26**: 571, 1953.

30. Barber, J. M., Magidson, O., and Wood, P.: Atrial septal defect, Brit. Heart. J. **12**: 277, 1950.

31. Brown, J. W.: Congenital heart disease, 1950, Staples Press, London.

32. Taussig, H. B.: Congenital malformations of the heart, 1947, The Commonwealth Fund, New York.

33. Lutembacher, R.: Sténose mitrale et communication interauriculaire, Arch. d. mal. du cœur **29**: 229, 1936.

34. Ferencz, C., Johnson, A. L., and Wiglesworth, F. W.: Congenital mitral stenosis, Circulation **9**: 161, 1954.

35. Schopf, D.: Das Syndrom von Lutembacher, Cardiologia **22**: 9, 1953.

WEBER-CHRISTIAN DISEASE WITH BONE INVOLVEMENT *

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Historical Review

Destructive bone changes have not been reported previously in Weber-Christian disease. However, Steinberg [1] has recently reported two cases with changes in the bone marrow.

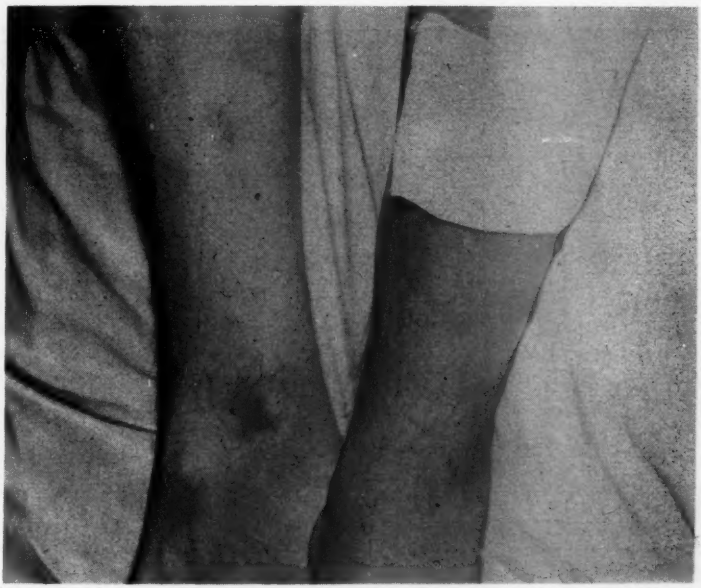

Fig. 1. View of legs showing typical subcutaneous nodule on medial surface of right ankle, and a discolored, depressed area of skin on the mid-leg, site of a former nodule which had regressed.

Pfeifer [2] in 1892 was the first to describe a patient with subcutaneous nodules in the extremities and trunk which were movable, red, painful, and associated with fever. A similar condition was reported by Gilchrist and Ketron [3] in an eight year old girl in 1916. In their patient the lesions were confined to the lower extremities and were associated with febrile episodes and loss of appetite. The contour of the legs was strikingly distorted, and on three occasions the

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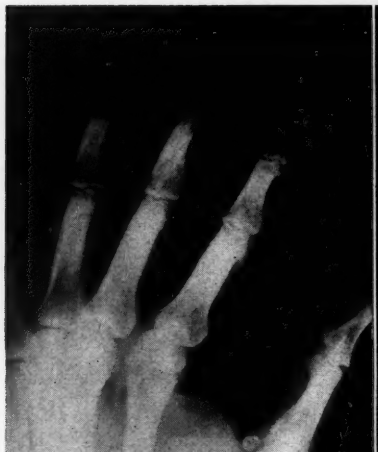
patient had a diffuse toxic erythema with swollen, painful joints. Histologically, phagocytosis of fat by macrophages was the outstanding feature. Weber [4] described the third case in 1925 and called it "relapsing nonsuppurative nodular panniculitis." His patient had nodules in both upper and lower extremities. Christian [5] in 1928 added "febrile" to Weber's terminology to emphasize an important feature of the disease, fever in recurring attacks. He described swollen, red, tender ankles during the patient's eighth and ninth exacerbations.

More than 50 additional cases have appeared in the literature to the present time. In most of these the process appeared to be limited to the subcutaneous fat. The disease is rarely fatal and few cases have been autopsied. Necropsies have shown that the process is not always confined to the subcutaneous fat, but



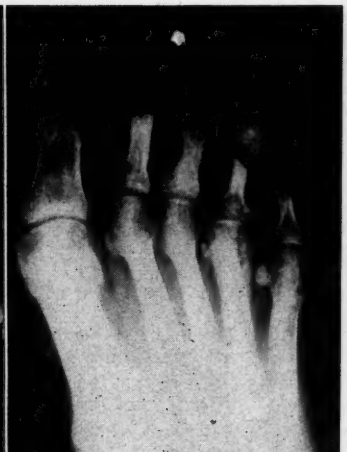


FIG. 2. FIG. 3.

FIG. 2. X-ray of right hand showing cystic destructive changes involving the shaft and cortex of the terminal phalanx of the right index finger.

FIG. 3. X-ray of the right foot showing similar destructive process involving the metatarsal phalangeal joint of the fourth right toe.

may have systemic involvement with changes in the perivisceral as well as the intravisceral fat.

The disease has been reported in infancy [6] as well as in the aged, and females are more commonly affected than males. Only one case has been reported in the Negro.[7]

The acute phase of the disease is characterized by recurrent crops of subcutaneous nodules which vary from 1 to 12 cm. in diameter, have a reddish purple color, and are slightly painful. During remissions the nodules may disappear or decrease in size. They leave a dimpling and a brownish pigmentation to the

overlying skin. In most cases the nodules do not ulcerate, but if they have been biopsied healing is prolonged. The subcutaneous nodules occur most commonly on the extremities and trunk, but may also involve the face, hands [8] and breasts.[9]

The systemic symptoms are variable, but fever and weakness are usually associated with the presence of the nodules. An acute attack of nausea, vomiting and abdominal pain attributed to gall-bladder disease was the first symptom in some reports,[10] while joint pains and tenderness have been mentioned during the course of the disease. In two case reports, one by Kennedy and Murphy [11] and a second by Brudno,[12] Weber-Christian disease developed during a recurrence of rheumatic fever in which migratory arthritis was present.

Histologically the process in the subcutaneous nodule goes through three phases. In the first there is an inflammatory reaction in the adipose tissue, with edema, congestion, and infiltration of polymorphonuclear leukocytes, lymphocytes, and macrophages. In the second phase there are necrosis of the fat cells and phagocytosis of the fat by macrophages. An occasional giant cell may be seen. In the final phase there is atrophy of the fat with connective tissue replacement. Small arterioles may show intimal proliferation and edema. Fatty infiltration of the liver and reticuloendothelial hyperplasia in the spleen may be present.

Steinberg [1] reviewed six autopsied cases and added two more of his own. In addition to the changes in the perivisceral and intravisceral fat previously reported, he demonstrated bone marrow involvement with patchy fibrosis, fat necrosis and lymphocytic infiltration. Spleen and lymph nodes showed follicular hypoplasia and reticulum cell hyperplasia. On the basis of his pathologic findings, and reviews of other autopsied cases, Steinberg has categorized systemic Weber-Christian disease into three forms. In the first type there are nodular lesions in the adipose tissue surrounding the abdominal organs, the mesentery and the omentum. The second shows areas of focal necrosis in the liver and spleen, but without perivisceral nodular lesions. The third has both perivisceral lesions and focal necrosis in the liver and spleen.

The etiology of the disease is unknown. Sensitivity to halogen compounds, particularly iodides and bromides, has been suspected. Focal infection, particularly of teeth and tonsils, has been present in numerous cases, and exacerbations of the disease have resulted after dental extractions.[13] No bacteria or virus has been consistently demonstrated. Because so many varied precipitating factors have been incriminated in the possible etiology, recent thinking postulates an antigen-antibody reaction in sensitized fatty tissue.

The differential diagnosis should include erythema nodosum, erythema induratum, the lipodystrophies, collagen disease, sarcoidosis, lymphomas, and enzyme-producing metastases from pancreatic carcinoma.

Case Report

A 42 year old white male was admitted to the Ohio State University Hospital on July 7, 1953, with a chief complaint of joint pains for seven months. He had been well until December 9, 1952, when he experienced nausea, vomiting and right upper quadrant pain lasting for three days. Two weeks later he noticed two tender nodules in the left achilles tendon, and weight bearing was painful because of a red, swollen, tender left big toe. The acute phase lasted two weeks, during which time he was

FIG. 4. High power photomicrograph of section through a subcutaneous nodule showing area of fat necrosis bordered by granulation tissue. The latter is composed of lymphocytes, histiocytes, multinucleated giant cells and capillaries.

unable to work. As the inflammation in the toe subsided the same process occurred in the proximal phalangeal joint of the fourth toe and lasted for one week.

During this time he was aware of several tender red lumps developing beneath the skin of the thigh and leg. The subcutaneous nodules and the pain in the left foot subsided, but shortly afterwards the right great toe and achilles tendon became red and swollen. The same nodules appeared in the soft tissue of the right thigh and leg. On April 7, 1953, he had three teeth extracted and two days later both heels

FIG. 5. Medium power photomicrograph of section through the cancellous bone of the proximal phalanx of the fourth right toe, showing fibrosis of the marrow spaces and granulomatous inflammation characterized by areas of fat necrosis surrounded by lymphocytes, macrophages and occasional multinucleated giant cells.

were sore again. The remaining teeth were extracted two weeks later because of chronic infection. There was a prompt exacerbation of joint symptoms and, for the first time, pain in the middle and terminal phalangeal joints of both hands, elbows, knees and right shoulder. He felt weak but had no knowledge of fever.

The positive physical findings were limited to the skin and skeletal systems. Throughout the subcutaneous tissue of both lower extremities there were multiple

erythematous nodules, 2 to 4 cm. in diameter. Over some of the areas the skin was depressed and had a red-brown color. The site of a biopsy performed several weeks prior to admission had not healed. Minimal swelling of all the fingers was evident. The terminal interphalangeal joint of the right index finger and the proximal joint of the left thumb were swollen, red and tender. Except for crepitation in the knee joints all other larger joints were grossly normal. A 2 plus pitting edema was present about the ankles and feet. The fourth right toe was swollen, red and exquisitely painful to touch. The great toes showed the same but less extensive changes.

The laboratory findings showed a leukocytosis of 10,050, with 64% polymorphonuclears, 22% lymphocytes, 12% eosinophils, 1% basophils and 1% monocytes. There were 4,300,000 red blood cells and 12.4 gm. hemoglobin. The sedimentation rate was 32 mm. (Wintrobe, uncorrected). Urinalysis revealed a trace of albumin and 10 to 12 white blood cells. The total serum protein was 6.3 gm.%, with 4.2 gm. albumin and 2.1 gm. globulin. The electrophoretic pattern was essentially normal. The serum calcium was 11.1 mg.%; phosphorus, 4 mg.%; alkaline phosphatase, 7.8 Bodansky units; acid phosphatase, 0.7 unit; sodium, 149.5 mEq.; potassium, 5.1 mEq.; chlorides, 107 mEq.; total cholesterol, 188 mg., with 78% esters; blood urea nitrogen, 13.5; fasting blood sugar, 92 mg. Three uric acid determinations were 4.1, 3.4 and 2.4 mg.%. The antistreptolysin titer was 166. Electrocardiogram and sternal bone marrow were normal. X-ray of the chest was normal. X-ray of the hands showed subcutaneous edema with cystic, destructive changes involving the shaft and cortex of the right index finger and left thumb. Similar destructive processes involved the metatarsal phalangeal joint of the fourth right toe. The radiologist considered gout, sarcoidosis and rheumatoid arthritis in the differential diagnosis.

Our initial impression was periarteritis nodosa. Dr. J. H. McCreary (consultant in dermatology) performed a punch biopsy of one of the subcutaneous nodules on the left leg. The pathologic report was lipogranuloma compatible with Weber-Christian disease. Dr. R. Wall (of the hematology division) studied the patient's peripheral blood, bone marrow and plasma protein electrophoretic pattern. There was no evidence to support a diagnosis of sarcoid, and no suggestion of primary or secondary hematopoietic disease. Electrophoresis showed only minor deviations from normal, namely, an elevated alpha 2 protein without concomitant elevation of alpha 2 lipoprotein.

During the patient's stay in our hospital he showed a temperature elevation which ranged from 99.6° to 101° F. He complained of severe joint pain, and required analgesics and narcotics for relief. Colchicine was given to toxicity without results. Following this he received cortisone (300 mg. first day, 200 mg. second day, 100 mg. third day), without improvement. Intravenous ACTH (50 mg. in 500 c.c. glucose in water given daily over an eight hour period for five days) made the joint pains worse. With the patient's consent the inflamed right toe was amputated just proximal to the metatarsal head. Fresh and fixed stained smears of scrapings from the metatarsal bone marrow failed to show any cellular material. Histologic sections showed areas of fat necrosis in the marrow. There was fibrosis of the adjacent tissue associated with an infiltration by lymphocytes, macrophages and multinucleated giant cells, all of which were interpreted by the pathologist as compatible with a diagnosis of Weber-Christian disease.

Summary

1. The historical background of Weber-Christian disease (chronic relapsing febrile nodular nonsuppurative panniculitis) has been reviewed.

2. A case is reported in which destructive bone involvement is described.

ACKNOWLEDGMENT

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SUMMARIO IN INTERLINGUA

Le morbo de Weber-Christian—etiam cognoscite como acute panniculitis febril nodular recidive non-suppurative—esseva primo describite in 1892. Illo es characterisate per recurrente greges de nodulos que pote occurrer in le texitos subcutanee, le texito adipose circa le organos abdominal, le hepate, le splen, e le medulla ossee. Le presente reporto include un patiente con alterationes destructive in un phalange del mano e un articulation phalango-metatarsal del pede. Le curso clinic del morbo esseva characterisate per recurrente greges de nodulos occurrente ubicunque al superficie del corpore e associate con febre, dolores visceral, nausea, vomito, e arthralgia.

Histologicamente le morbo se manifesta per alterationes inflammatori in le texitos adipose, con necrosis de grassia e le presentia de cellulas gigante. Le prime characteristicas pathologic es sequite per fibrosis e cicatrisation concave. Es notate in le litteratura le occurrentia de sensibilitate a compositos halogenic, drogas, infectiones, e altere agentes. Isto pare indicar que le causa fundamental es un reaction de antigeno e anticorpore in sensibilisate texitos adipose. Le morbo se incontra in patientes de omne etates. Illo es plus frequente in feminas que in masculos. Solmente un caso de un patiente negre es traciabile in le litteratura.

Le patiente in nostre caso esseva un masculo blanc de 42 annos de etate. Ille habeva generalisate nodulos dermatic de 7 menses de duration, associate con ardente, turgescente articulationes e plure areas de cicatrisation concave. Degeneration cystic de plure phalanges esseva constatate per roentgenographia. Le hemogramma, varie conditiones hemochimic, observationes electrophoretic, e studios del medulla ossee esseva essentialmente normal. Biopsias dermatic e ossee, del altere latere, revelava le classic aspectos histologic de necrosis adipose, con macrophagos, cellulas gigante, e alterationes inflammatori que esseva compatibile con le diagnose de morbo de Weber-Christian. Le tractamento con colchicina, cortisona, e ACTH remaneva sin effecto.

BIBLIOGRAPHY

1. Steinberg, B.: Systemic nodular panniculitis, Am. J. Path. **29**: 1059, 1953.
2. Pfeifer, V.: Ueber einen Fall von herdweiser Atrophie des subcutaneous Fettgewebes, Deutsches Arch. f. klin. Med. **50**: 438, 1892.
3. Gilchrist, T. C., and Ketron, L. W.: A unique case of atrophy of the fatty layer of the skin, preceded by the ingestion of the fat by large phagocytic cells-macrophages, Bull. Johns Hopkins Hosp. **27**: 291, 1916.
4. Weber, F. P.: A case of relapsing nonsuppurative nodular panniculitis showing phagocytosis of fat cells by macrophages, Brit. J. Dermat. **37**: 301, 1925.
5. Christian, H. A.: Relapsing febrile nodular nonsuppurative panniculitis, Arch. Int. Med. **42**: 338, 1928.
6. Larkin, V. deP., DeSanctis, A. G., and Margulis, A. E.: Relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian disease). Review of the literature with report of a case, Am. J. Dis. Child. **67**: 120, 1944.
7. Johnson, W. A., and Plice, S. G.: Relapsing febrile nodular nonsuppurative panniculitis: report of a case with review of literature, Arch. Path. **48**: 281, 1949.
8. Bunnell, I. L., and Levy, D. S.: Weber-Christian's disease: report of a case, Ann. Int. Med. **28**: 169, 1948.

9. Binkley, J. S.: Relapsing febrile nodular nonsuppurative panniculitis, J. A. M. A. **113**: 113, 1939.
10. Koch, L. C.: Relapsing nodular panniculitis (Weber-Christian disease), Am. Prac. and Digest. Treat. **2**: 1013, 1951.
11. Kennedy, R. J., and Murphy, L. R.: Weber-Christian disease, Am. J. Med. **6**: 672, 1949.
12. Brudno, J. C.: Chronic relapsing febrile nodular nonsuppurative panniculitis, New England J. Med. **243**: 513, 1950.
13. Miller, J. L., and Kritzler, R. A.: Nodular nonsuppurative panniculitis, Arch. Dermat. and Syph. **47**: 82, 1943.

CONSTITUTIONAL HEPATIC DYSFUNCTION—FAMILIAL NONHEMOLYTIC JAUNDICE*

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MOST patients with jaundice are considered to have either organic disease of the liver or biliary passages or hemolytic disease. Occasionally one sees a patient who does not fall into either of these two groups.

CASE REPORT

A 26 year old male student for the ministry was examined in September, 1951, because of persistent jaundice. He had been well until 1943, at which time he developed diarrhea and was found to be jaundiced. He was put to bed for two weeks. During this time his icterus and diarrhea gradually subsided. Since then he has had frequent exacerbations of jaundice, accompanied by weakness, lassitude, anorexia, diarrhea and occasionally pain in the right upper quadrant. He entered the service and was able to serve throughout the war without difficulty. In 1949, because of recurrent episodes of jaundice, an exploratory laparotomy was performed at another hospital. Prior to surgery, liver function studies were said to be normal, and a cholecystogram showed a normally functioning gall-bladder. The laparotomy was said to have revealed a normal gall-bladder and bile ducts. A cholangiogram was interpreted as being normal, and liver biopsy was reported to show normal liver tissue. Following surgery he continued to have frequent exacerbations of his symptoms. After the war he applied for entrance to medical school but was turned down because of "progressive liver disease." Because of persistent symptoms he presented himself for further evaluation.

Physical examination revealed a somewhat asthenic young white male with an icteric tint to his sclerae. The eyes, ears, nose and throat were negative. The neck was supple. The heart and lungs were not remarkable. The liver and spleen were thought initially to be palpable; however, on subsequent examinations they could not be felt. There was a well healed surgical scar in the right upper quadrant. Neuromuscular examination was negative.

Laboratory studies revealed a hemoglobin of 15.5 gm.; red cell count, 5,120,000; hematocrit, 46. The white cell count was 7,100, with 57 neutrophils and 43 lymphocytes. The urine was alkaline, with a specific gravity of 1.010. There was a trace of albumin, but subsequent tests were negative. The urine was negative for sugar and bile, and the microscopic examination was negative. The nonprotein nitrogen was 32.5 mg.%. Serologic test for syphilis was negative. The prothrombin

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concentration was 100%. The cephalin flocculation was 1 plus and 0. The alkaline phosphatase was 2.4 Bodansky units. The total protein was 7.0 gm.%, with an A/G ratio of 4.6 to 2.4. The cholesterol was 214 mg.%, with 75 mg.% free and 139 mg.% esters. Bromsulphalein excretion test showed 5% retention in 45 minutes. The serum bilirubin was 0.3 mg.% direct and 3.6 mg.% total. The 24 hour urine urobilinogen was 1.4 mg. The fecal urobilinogen was 55.4 mg. per day and 172.5 mg. per day. Reticulocyte counts were 1.5% and 1.8%. Fragility test with hypotonic saline showed initial hemolysis at .44% and complete at .32%. The Coombs' test was negative.

The patient's family was also investigated for jaundice. The father gave a history of having been jaundiced as a young man. Two brothers and one sister had definitely elevated icterus indices. These findings are shown in table 1.

This patient meets the criteria for the diagnosis of familial nonhemolytic jaundice. The absence of liver disease was demonstrated by the normal liver function tests and by the negative gall-bladder series. Liver disease was further ruled out by the negative gall-bladder exploration and by the negative liver biopsy. Hemolytic anemia was also ruled out satisfactorily. There was no anemia and no reticulocytosis. Furthermore, the red cells were shown to be normal by the absence of abnormal fragility, negative Coombs' test and absent spherocytosis.

TABLE 1

	Icteric Index	History of Jaundice
Father	7.4	Yes
Mother	9.4	No
Sister (W. T.)	9	No
Sister (M. T.)	15	No
Sister (V. P.)	9.4	No
Brother (H. M.)	19	No
Brother (E. M.)	22	No
Brother (D. M.)	9.2	No
Brother (T. M.)	10.7	No

The familial tendency was established by the finding of a definitely elevated icterus in three of the siblings. The patient's symptomatology—fatigue and vague digestive disturbances—has in large measure been relieved by a simple explanation of the nature of his trouble and assurance of the benign nature of the condition.

This condition was first described by Gilbert [1] in 1902. Since then there has been frequent mention of the disease in the European literature. For some reason there has been but scant reference to this condition in American writing. In 1935 Rozendaal, Comfort and Snell [2] reviewed 214 cases of jaundice with an "indirect" type of serum bilirubin. Of these cases, 48 showed evidence of neither liver disease nor hemolytic disease, and they considered these patients to fall into the group of constitutional hepatic dysfunction. In 1941 Dameshek and Singer [3] reported two families with this type of jaundice, and coined the term "familial non-hemolytic jaundice." Meulengracht [4] in 1947 reported 35 cases from his own practice. Since then there has been no further mention of the condition in American or English journals.

Constitutional hepatic dysfunction is a benign process. Extensive liver function tests in both Dameshek's and Comfort's cases showed no evidence of disease of either the liver or the biliary tract. In our case, exploration of the biliary tract and liver biopsy had been carried out with negative findings. The

basic lesion is thought to be a congenital inability of the hepatic cells to excrete bilirubin. This was demonstrated by Dameshek and Singer [3] by the bilirubin excretion test. In both their frank and latent cases there was a definite delay in the excretion of injected bilirubin. Furthermore, the benign course has been demonstrated by long term follow-ups of many of these people.[4]

In spite of the benign nature of the process there is a definite symptomatology. All authors stress the same symptoms—asthenia, fatigue and digestive disturbances. The mechanism of these complaints is not apparent, as bilirubinemia per se is asymptomatic. Comfort et al. observed that exacerbations of the process were associated with emotional upsets and with minor ailments such as respiratory infections. In Dameshek's and Singer's series the women were more aware of the condition and had more functional complaints than did the men. Many of Meulengracht's patients' symptoms cleared with reassurance. This was also true in our case. The average layman associates jaundice with biliousness. Furthermore, biliousness, malaise, constipation and gas are all associated together. Possibly the symptomatology is more closely related to the patient's concept of his condition than to any effect of the hepatic dysfunction. This idea is supported by the fact that those who are unaware of their jaundice are usually asymptomatic. None of the siblings of our case was aware of this affliction, and each considered himself to be in good health.

The diagnosis of this condition is a diagnosis of exclusion. It is most frequently confused with hemolytic anemia. Occasionally cases of mild hemolytic anemia between crises show neither anemia nor reticulocytosis. However, these people regularly show an increased fecal urobilinogen. A normal fecal urobilinogen should rule out this diagnosis. Liver disease also must be ruled out. This can be done without too much difficulty. In the jaundiced patient a normal gall-bladder, x-ray and normal liver function test should rule out disease of the liver and biliary tract. The demonstration of a familial tendency further establishes the diagnosis. This finding is by no means essential, as in many cases a familial trait was not demonstrable.

In contrast to the infrequent reports in the literature, the large group of cases reported by Comfort et al. and by Meulengracht suggest that many cases must be undiagnosed or misdiagnosed. The good prognosis of this condition makes it essential to separate these cases from the more serious forms of jaundice. The reason for this is readily apparent. Our patient was subjected to an unnecessary exploratory laparotomy. Furthermore, he was denied entry to a medical school because of "progressive liver disease." Explanation of his disease resulted in relief of his symptoms.

Summary

Constitutional hepatic dysfunction or familial nonhemolytic jaundice is a benign condition characterized by jaundice without evidence of hemolytic disease or organic liver disease. A case has been presented and the literature reviewed. The importance of accurate diagnosis has been stressed.

Acknowledgment

We wish to acknowledge the assistance of Dr. G. Watson James in the study of this case. Dr. H. D. Miller, of Johnson City, Tennessee, kindly obtained the icteric indices of the patient's family.

SUMMARIO IN INTERLINGUA

In le majoritate del casos on classifica patientes de ictero como suffrente de morbo del hepate o del via biliari o de morbo hemolytic. De tempore a tempore on trova un patiente con ictero qui pertine ni al un ni al altere de ille classes. Un tal caso es reportate in le presente articulo. Le condition in question ha frequentemente essite discutite in le litteratura europee sed plus tosto rarmente in le litteratura statounitese. Illo esseva primo describite per Gilbert in 1902 e ha recipite le nomine de "dysfunction hepatic constitutional." Illo ha etiam essite appellate "ictero non-hemolytic familial." Le condition es benigne. Le symptomatologia clinic corresponde a episodios periodic de ictero. Le patientes se plange de dyspepsia e asthenia. Studios laboratorial revela un typo indirecte de bilirubinemia. Le absentia de hemolyse es manifeste per le absentia de anemia e reticulocytosis e le normalitate de urobilinogeno fecal. In plus, studios del functionamento hepatic revela nulle signo de morbo del hepate. In le caso hic reportate, biopsia del hepate habeva essite executate sed nulle evidentia de morbo parenchymal esseva notate. Exploration chirurgic etiam revelava nulle obstruction extrahepatic.

Le diagnose se face per exclusion. Frequentemente il es possibile demonstrar un tendentia familial, lo que reinfortia le diagnose. Le patiente del presente reporto pertineva a un grande familia. Su parentes e su 7 fratres e sorores esseva reportatemente normal, sed pro 3 de istes le presentia de definitemente elevate indices icteric esseva establite.

A causa del excellente prognose il es importante recognoscer iste condition e differentiar lo ab plus serie formas de ictero. Le patiente del caso hic reportate habeva essite subjicite a un non-necesse intervention chirurgic; su application pro admission a un schola medical habeva essite rejicite; e ille se trovava in un disturbate stato emotional. Un simple explication de su difficultate, insimul con reconfortation, resultava in le complete alleviamento del symptomas.

BIBLIOGRAPHY

1. Gilbert, A., and Lereboullet, P.: La cholemie simple familiale, Gaz. hebd. de méd. **49**: 887, 1902.
2. Rozendaal, H. M., Comfort, M. W., and Snell, A. M.: Slight and latent jaundice, J. A. M. A. **104**: 374 (Feb. 2) 1935.
3. Dameshek, W., and Singer, K.: Familial non hemolytic jaundice, Arch. Int. Med. **67**: 259 (Feb.) 1941.
4. Meulengracht, E.: A review of chronic intermittent juvenile jaundice, Quart. J. Med. **16**: 83 (Apr.) 1947.

AN ELECTROCARDIOGRAPHIC LOG OF RECURRENT HYPERKALEMIA IN A SEVERELY WOUNDED MAN *

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SOON after the outbreak of the Korean War it became apparent that the clinical syndrome of potassium intoxication and severe azotemia was responsible for a considerable number of deaths in soldiers who had survived their initial

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injuries and associated complications. A detailed study of the metabolic effects of potassium derangements in this group of previously healthy individuals was begun early in 1952 by a special research unit. Various diagnostic and therapeutic methods were utilized and evolved during the course of this activity and are being reported on in more detail elsewhere.[1, 2, 3, 4] The electrocardiogram as a diagnostic tool and the technics for electrolyte adjustment, including the Kolff method of artificial hemodialysis,[5] proved indispensable in the management of such problems.

One of the most instructive cases, and one which typifies the procedures used in diagnosis and management, is presented below. Noteworthy in this case are the recurrent bouts of hyperkalemia, and their uniform appearance as graphically recorded by the electrocardiogram and verified by biochemical studies.

In the discussion to follow the QTc is the QT interval in seconds as corrected for rate by the method of Taran and Szilagyi.[6] The normal is 0.39 ± 0.02 second.

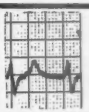
Case Report

A 26 year old infantryman was blown from his bunker into a mesh wire at 6 a.m. on February 24, 1953, by an incoming enemy artillery round. Immediately incurred were severe wounds of the left leg, left arm, abdomen and head, with traumatic amputation of the right leg and a portion of the right buttock. Within a few minutes he was transferred to an Aid Station, where he arrived in an unconscious state, in deep shock with an unobtainable blood pressure. Eighteen hundred cubic centimeters of saline and serum albumin were rapidly given, and in one and one-half hours the blood pressure was reported as 80/40 mm. of Hg. He was then transferred to an Army Surgical Hospital, where in the next 10 hours a total of 6,000 c.c. of type O (low agglutinin titer) Rh negative blood was given, and the blood pressure varied between 100/70 and 145/80 mm. of Hg. There was a persistent tachycardia and the patient remained comatose.

At 4 p.m. an abdominal laparotomy was performed. Metallic fragments were removed from the right kidney, and both the lower pole of the right kidney and the liver were noted to be severely traumatized. During the operative procedure, which lasted four hours, another 4,500 c.c. of a similar type of whole blood were given. The blood pressure was maintained above 90/60 mm. of Hg throughout and after the procedure with the aid of norepinephrine. On February 24 the total urine output was recorded as 400 c.c.

In the following 36 hours the comatose state persisted, probably from severe cerebral concussion. The blood pressure remained at about 120/70 mm. of Hg, a tachycardia of 130 persisted, and a fever to 103° developed. On February 25 the total urinary output was 175 c.c. of smoky reddish amber urine, containing many red blood cells and much protein.

On February 26, at 3:30 p.m., the patient was transferred to the Renal Insufficiency Center, 11th Evacuation Hospital. Upon admission the blood pressure was 140/80 mm. of Hg; pulse, 110; respirations, 30; oral temperature, 101.2°F. The patient was semicomatose but reacted with all extremities to painful stimuli. Occasional spontaneous movements occurred. The state of hydration was adequate. The chest was clear except for a few inspiratory rhonchi; the heart sounds were normal. Peristaltic sounds were heard in the abdomen about the recently sutured surgical incision. There was a traumatic amputation of the right leg high on the thigh, and considerable necrotic tissue was present at the amputation site. There were multiple small and large wounds on the left leg, back and both arms. An admission electrocardiogram (figure 1) revealed minimal peaking (tenting) of the precordial T waves,

	A	B	C	D
Date & Time	26 Feb 1550 hrs	28 Feb 0845 hrs	28 Feb 1945 hrs	1 Mar 0330 hrs
K mEq/L	7.1	7.7	8.2	4.2
NPN mgm %	114	276	284	104
QRS duration	0.07	0.10	0.13±0.02	0.06
QTc	0.36	0.42	0.49	0.39
LEAD I				
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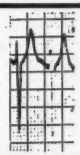
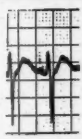
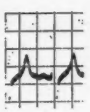
LEAD V5				
LEAD V6				

FIG. 1.

suggestive of mild serum potassium elevation. The initial blood chemistries are recorded in chart 1.

Course: The patient had a protracted and stormy course, extending for 17 days following arrival at the Renal Insufficiency Center. During this time he had four distinct and recurrent bouts of potassium intoxication; three were relieved with the

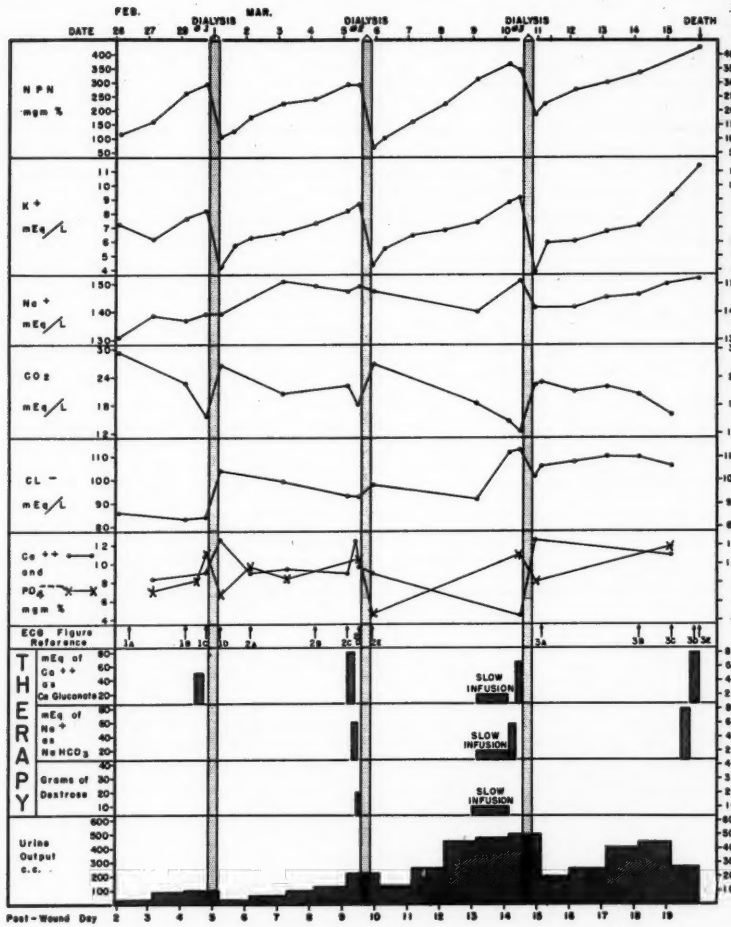


CHART 1.

aid of artificial hemodiolysis, the fourth was fatal. Oliguria was marked throughout the course. The maximal daily urinary output was 500 c.c. on the fourteenth post-wound day; the total output diminished somewhat on the succeeding days, due largely to recurrent bouts of shock and severe toxemia.

Some of the details of the course were as follows: Soon after admission a tracheotomy was performed to minimize impending and developing pulmonary complications. Following an initial mild drop in the serum potassium (chart 1), the potassium and nonprotein nitrogen levels progressively increased and the electrocardiogram showed the characteristic pattern of hyperkalemia (figure 1). At 8 p.m.

on February 28 the serum potassium was 8.2 mEq. per liter, and the patient was in a critical state. Sixty cubic centimeters of 10% calcium gluconate (134 mEq. of calcium ion) were rapidly injected intravenously. The antagonistic effect of the calcium ion on the serum potassium was immediately observed in an improved electrocardiogram, and the patient was readied for dialysis. In two hours the beneficial effects of the calcium therapy began to diminish, the evidences of hyperkalemia again

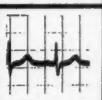
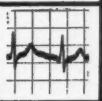
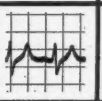
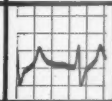
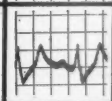
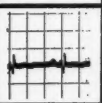
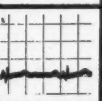
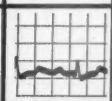
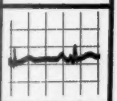
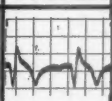
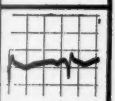
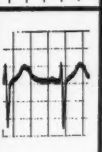
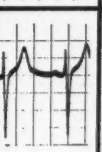
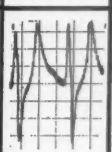
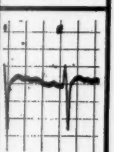
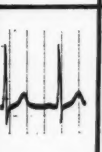
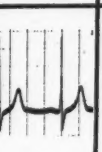
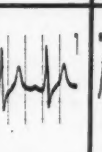
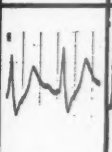
	A	B	C	D	E
Date & Time	2 Mar 0855 hrs	4 Mar 0900 hrs	5 Mar 0845 hrs	5 Mar 1300 hrs	5 Mar 2310 hrs
K mEq/L	6.3	7.3	8.2	9.0	4.3
NPN mgm %	171	246	295	—	74
QRS duration	0.07	0.08	0.10	0.13	0.08
QTc	0.39	0.40	0.42	0.49	0.37
LEAD I					
LEAD II					
LEAD III					
LEAD AVR					
LEAD V3					
LEAD V5					

FIG. 2.

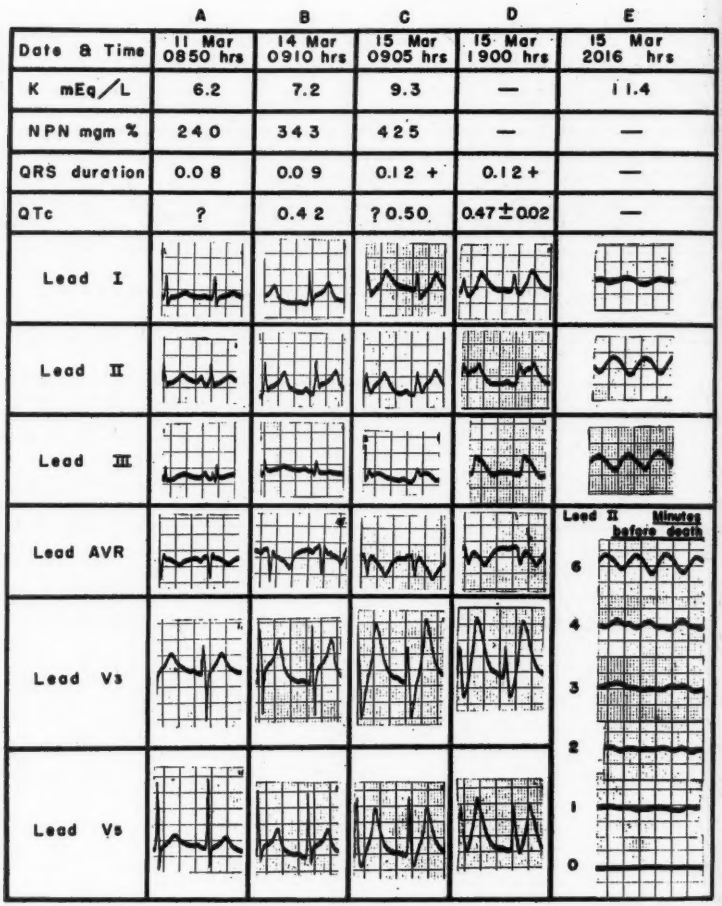


FIG. 3.

became apparent on the electrocardiogram, and dialysis was begun at 10 p.m. Following a six-hour dialysis an excellent chemical and cardiographic result was obtained (chart 1 and figure 1D), but there was little change in the patient's general condition. He remained comatose and unresponsive. He was given small amounts (up to 400 c.c. daily) of 10% glucose with added vitamins. No other nourishment was administered. He began to lose weight rapidly.

On March 2 the patient began to have periods of semilucidity and to answer some questions. This state lasted for one week. On March 3 an attempt was made to debride, under anesthesia, some of the extensive necrotic wounds, since it was felt that they were contributing significantly to the severe toxemia and continued oliguria.

Prior to this time such procedures were impossible because of the patient's critical condition. The anesthesia was tolerated well, but the freshly debrided wounds began to bleed actively and many vessels had to be ligated. During the procedure a total of 3,000 c.c. of whole blood (including 1,500 c.c. freshly donated) and 200 c.c. of serum albumin was necessary to replace the losses and maintain the blood pressure above shock levels.

Recurrent and progressive hyperkalemia and azotemia developed in association with pronounced oliguria, which on two occasions measured only 20 c.c. in a 24 hour period. On March 5 the serum potassium had again risen to intoxicating levels (figures 2C and 2D), and emergency "holding" measures were instituted until the artificial kidney which was in use at the time could be readied for the patient.

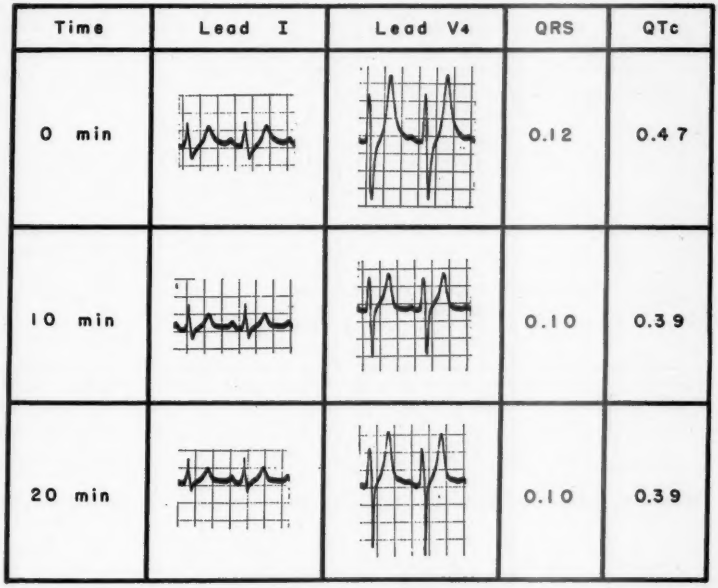


FIG. 4. The effect of one rapid intravenous injection of 30 c.c. of 50% dextrose and 15 units of regular insulin given from 0 min. to 2 min. The serum K^+ was 8.6 mEq./L. before injection.

Ninety cubic centimeters of 10% calcium gluconate (201 mEq. of calcium ion) produced a marked reversal of the electrocardiogram toward normal and an improvement in the patient's general condition. The salutary effect persisted for one and a half hours, and then rapid deterioration of the electrocardiogram again became apparent. Sodium ion as $NaHCO_3$, 60 c.c. of a 7.5% solution (53 mEq. of sodium ion), given intravenously in a single injection, again improved the appearance of the electrocardiogram, but the beneficial effect was also short-lived. Finally, one hour before dialysis was begun, 30 c.c. of 50% glucose with 15 units of regular insulin added also improved the appearance of the electrocardiogram (figure 4), and the second dialysis was begun at 5:15 p.m. Again there was an excellent chemical and

electrocardiographic result to dialysis (chart 1 and figure 2E), and the patient was clinically somewhat improved. Oliguria persisted but was less intense than previously.

On March 8 the patient suddenly went into shock. No source of bleeding could be found, and the blood pressure was finally elevated and stabilized after transfusion of 2,200 c.c. of whole blood. Recurrent hyperpotassemia and azotemia appeared, and by the fifth day after the second dialysis, on March 10 (the fourteenth post-wound day), the serum potassium was 9.2 mEq. per liter and the nonprotein nitrogen was

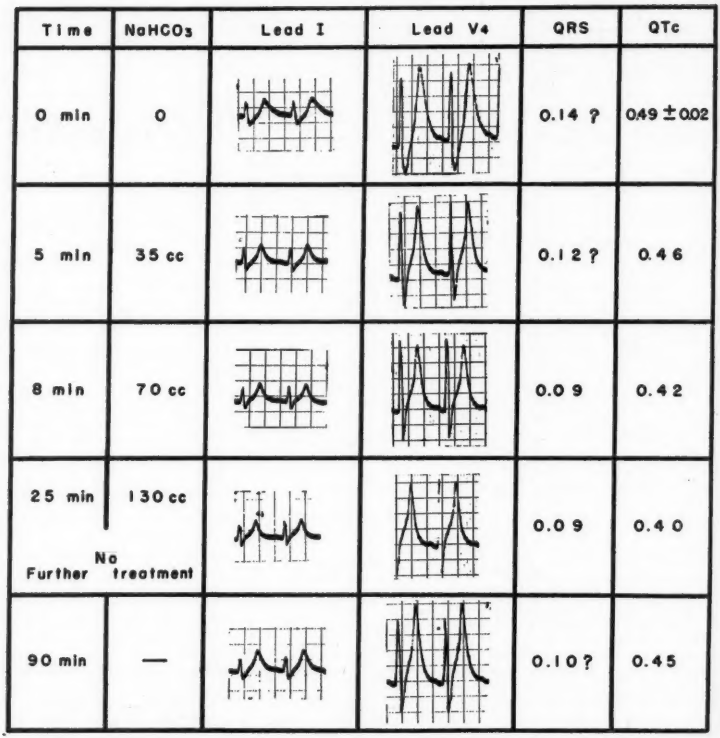


FIG. 5. The effect of fairly rapid intravenous infusion of 130 c.c. of 7½% $NaHCO_3$ (115 mEq. of Na^+). Note the very prompt reversion of the electrocardiogram toward normal and the partial deterioration one hour after discontinuance of therapy. At 25 min. the serum K^+ was 8.3 mEq./L.

367 mg. %. Rapid intravenous injections of both sodium bicarbonate and calcium gluconate (chart 1) brought about the desired reversal effect for several hours. A third dialysis, beginning at 11:30 a.m. on March 10, produced only a transitory decline in the serum potassium and only a partial reduction in the nonprotein nitrogen.

There was no obvious improvement in the very poor clinical appearance. Despite judicious antibiotic therapy a diffuse pneumonitis appeared, and on March 12 a pericardial friction rub was detected. This was also manifest in the electro-

cardiogram as ST segment deviations (figure 3). The patient remained comatose, with marked respiratory difficulty. He had lost an enormous amount of weight in the two and one-half weeks since his injury and was in a very grave state. The nonprotein nitrogen and serum potassium rose more rapidly on this occasion than before (chart 1), and by the fourth day following the third dialysis the potassium was 9.3 mEq. per liter (figure 3C), and the nonprotein nitrogen was 425 mg. %.

As on previous occasions, intravenous sodium bicarbonate (130 c.c. of 7.5%, or 115 mEq. of sodium ion) gave immediate but temporary relief (figure 5), with

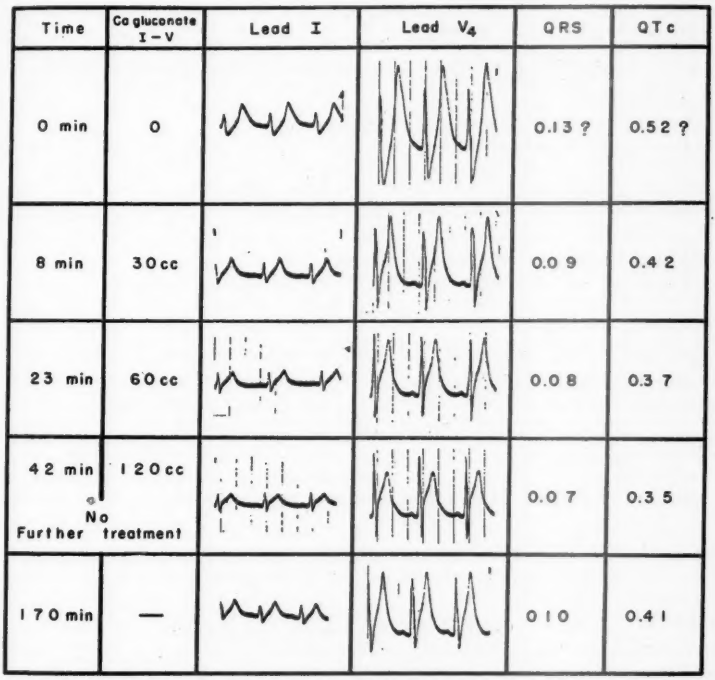


FIG. 6. The effect of fairly rapid intravenous infusion of 120 c.c. of 10% calcium gluconate (268 mEq. of Ca^{++}) on the electrocardiogram. Note the alterations in the QRS and QTc and the fairly lasting effect after cessation of treatment. The K^+ value was 9.0 mEq./L. at the end of the therapy.

significant transient reversion of the QRS and QTc to normal or near-normal values. Following the reappearance of severe electrocardiographic alteration, calcium gluconate (120 c.c. of a 10% solution, or 268 mEq. of calcium ion) also gave an immediate and lasting effect on the electrocardiogram (figure 6), so that in the six hours following calcium ion administration there was only gradual recurrent deterioration of the electrocardiographic appearance. Throughout the final 48 hours the patient's blood pressure was low and unstable, and it did not respond to the usual therapeutic measures. Pulmonary edema and Cheyne-Stokes respiration developed.

and because of his very critical and unstable condition it was obvious that he could not withstand even the initial preparations for a fourth dialysis. Terminal electrocardiographic recordings showed the effects of severe potassium intoxication (figures 3D and E), and he died at 8:24 p.m. on March 15, the nineteenth post-wound day. A terminal serum potassium (heart blood immediately post morten) was 11.4 mEq. per liter.

A summary of the gross and microscopic necropsy findings consisted of:
Acute renal tubular necrosis
Bronchiolar pneumonia, focal, bilateral
Focal edema and necrosis of the myocardium
Acute fibrinopurulent pericarditis
Central necrosis of the liver
Acinar dilatation of the pancreas
Acute cystitis
Adrenal lipoid depletion with tubular atrophy
Parathyroid hypertrophy
Necrosis of occipital cortex bilaterally, probably traumatic
Traumatic amputation, right leg, with fracture of right femur
Penetrating wounds, abdomen, with laceration of the liver and lower pole of right kidney
Penetrating wounds, pelvis, back, left thigh
Superficial wounds, scalp

Discussion

It has now been well established that elevation of the potassium concentration in extracellular fluid in persistent oliguria may lead to intoxication by potassium ion, to which the patient's death is directly attributable. Among the chief causes for acute oliguria (lower nephron nephrosis) are severe trauma and muscle crushing injuries, hemolytic transfusion reactions and nephrotoxins. Severe trauma presents one of the most difficult problems because one has to deal with a critically ill patient, at times suffering from overexposure to cold, often in shock, requiring multiple transfusions and having suffered muscle and other organ traumatizing injuries. The necessity for wound surgery and hemostasis adds further insult to the existing critical state. Under such a set of circumstances, acute renal shutdown is a fairly frequent occurrence and has been observed in a significant number of patients following extensive war wounds. Injury of a similar magnitude may occur in civilian practice, usually as the result of industrial or automobile accident, but the factor of exposure is rarely so prominent. In the event of a major atomic catastrophe in an American city one could anticipate a large number of cases similar to the one which is the subject of this paper.

The present case illustrates in detail many of the problems involved in the management of severe post-traumatic oliguria. There was no evidence of incompatible transfusion reaction. The initial profound shock and the unstable blood pressure were evidences of the fragile clinical condition, as was the persistent state of reduced consciousness which was the result of cerebral contusion and probably significant initial cerebral anoxemia incident to the shock. The extensive degree of muscle tissue destruction, the subsequent infection and necrosis of more tissue at the margin of all wounds, the accelerated catabolism of

protein tissue, and the moderate amount of injury to the liver and kidney, all contributed to the renal damage, the shock and the rapidly recurrent azotemia and potassium intoxication.

The oliguria was apparent early and the serum potassium elevation rapid in this case; these were undoubtedly due to the multiplicity of factors operating as described above. Often the renal shutdown is much less apparent and the development of hyperkalemia much slower. Potassium intoxication following severe trauma rarely appears before the fifth day (except where intravascular hemolysis has also occurred). In the present case it developed in a few hours less than five full days.

With reference to chart 1, it is interesting to note the biochemical course of the disease in this patient. The graphic development of recurrent potassium rise and azotemia following the initial injury and after each dialysis is quite repetitious, both in rate of rise and time duration, and they could nearly be superimposed on each other. It will be noted that following the third and final dialysis the serum potassium rose rapidly and the nitrogenous products did not drop to their previously low post-dialysis level. The recurrent rapid biochemical intoxications in this patient are a direct reflection of the severity of the clinical state. In patients severely oliguric but with less extensive tissue destruction and infection, one rarely needs more than one dialysis or, when two are required, they are at much more widely spaced intervals.

It is particularly interesting to note that the curve of potassium rise in each of the four separate intoxication episodes in this patient tends to take a sigmoidal shape. There is an initial rapid rise from the subnormal, immediate post-dialysis serum values which probably reflects the reëstablishment of some type of equilibrium state following the marked alterations produced by dialysis. There follows a plateau phase, lasting in each instance three to four days, in which there is a slow, progressive elevation of serum potassium. Finally, on about the fifth day following the previous dialysis, there is a recurrent rapid upswing in the level of the serum potassium. In the present patient this third phase was interrupted on three occasions by dialysis, and in the fourth, without dialysis, lethal levels were rapidly reached. In the third phase the sudden deterioration of the patient, chemically, electrocardiographically and clinically, was on each occasion accompanied by acidosis, during which the CO_2 fell to between 13 and 18 mEq. per liter. It is possible that the acidosis, by altering the cell membrane potassium equilibrium, precipitated the abrupt progression of potassium intoxication. Once the patient enters this accelerated phase he must be under constant observation, with frequent electrocardiographic evaluation. In contrast to the sigmoidal potassium curve, the serum nonprotein nitrogen tends to increase in a straight line (chart 1).

It is further noted that the serum sodium level has usually remained within a normal range and does not vary with the potassium. The reason for this is not clear. When serum sodium levels do fall, they are most difficult to raise by parenteral therapy, and the hazard of pulmonary edema limits the extent to which one can use such therapy. The serum calcium and phosphorus concentrations are noted generally to vary inversely, but, whereas hyperphosphatemia (above 6 mg. %) is present almost throughout the course and closely parallels the serum potassium concentration, the expected hypocalcemia was rarely of

significant degree. This is because of the frequent administration of calcium ion as a therapeutic agent.

The serum carbon dioxide and chloride levels have been graphed in chart 1. In general, the serum chloride has remained within fairly normal confines. The CO_2 drops, however, as the clinical condition becomes more severe, and in general it varies inversely with the serum potassium and the progressive azotemia. This is a reflection of a progressive metabolic acidosis, since the serum pH also falls at this time. The implications of such an acidosis on the serum potassium and the general ionic equilibrium have already been mentioned.

The electrocardiogram has proved to be an indispensable aid in the management of hyperkalemia, especially in the severely traumatized man where the serum potassium may rise very rapidly to intoxicating levels. Although it has been observed on many occasions that there is no direct correlation from patient to patient between the level of the serum potassium and the electrocardiographic appearance, from cases such as the one described above it can be stated that within very limited confines the serum potassium level can be predicted from the electrocardiographic tracings taken in recurrent hyperkalemia when such tracings are compared with similar ones during a previous bout of potassium elevation in the same patient. In other words, there may be considerable variation in the appearance of the electrocardiogram among a group of patients at a given level; for example, 7.5 mEq. per liter of potassium elevation, but in a single patient during recurrent hyperkalemia the electrocardiographic tracings would be practically identical and predictable at any comparable level (figures 1, 2 and 3). In the present case, evidence of potassium elevation first appeared on the electrocardiogram at a serum potassium level of 7.1 to 7.4 mEq. per liter (figure 1).

The serial evolution of electrocardiographic alterations in progressive hyperkalemia has been described in detail elsewhere,[2, 7, 8] and will be summarized briefly here. The sequence of changes seen is: (1) An elevation and peaking of the T waves, most readily seen in the mid-precordial leads (figure 1A), and usually at serum potassium levels above 6.5 mEq. per liter. (2) Broadening of the QT interval (QTc), which is progressive throughout all stages of alteration and is a function at least of serum calcium depression. (3) Widening of the "S -ST" angle and gradual loss of the ST segment so that the S wave blends with the ascending limb of the T wave. This change is first seen in limb Leads I and II (figures 2B, C and D). (4) Widening of the QRS complex, with often a terminal delay in activation (depolarization) of the base of the right ventricle suggestive of right bundle branch block (figures 1 and 2). This is most easily observed and measured in unipolar lead aVR and standard Lead II. (5) Variable prolongation of the PR interval, with eventual loss or blending of the P wave into the preceding T wave (not present in this case). (6) Disintegration of the ventricular complexes into the near-terminal "sine" wave of ventricular fibrillation (figure 3E). (7) Ventricular asystole.

It can be stated unequivocally that clinical evidences of hyperkalemia do not exist without significant and characteristic alterations in the electrocardiogram. Serum potassium determinations are of value in the detailed evaluation of the patient's status but are not absolutely necessary for clinical management. Since the electrocardiogram is influenced by the total ionic pattern of the extracellular

fluid, it follows that the recorded reactions of the cardiac muscle are direct indications of the ionic environment acting at the muscle cell membrane.[8] Consequently, the electrocardiogram provides more information than do the serum concentrations of one or two electrolytes.

It has been our policy to take an electrocardiogram (six limb leads and six precordial leads) on a direct-writing machine once or twice daily during the early stages of potassium elevation. When near-critical levels are reached, a short segment of limb Lead II and V_4 is obtained every few minutes and an occasional complete tracing recorded. During parenteral therapy, either continuous or very frequent tracings (every one or two minutes) of a selected lead (usually limb Lead I or II and V_4) are recorded. By these methods an extremely close vigilance can be maintained at the bedside and immediate decision made as to the necessity for more parenteral therapy or for artificial hemodialysis. The clinical appearance of the patient rarely affords clues for such decisions, and chemical determinations of electrolyte concentrations are frequently too long delayed to be of great value in such situations.

The treatment of the oliguric hyperkalemic patient has been discussed in more detail in associated publications,[1, 2, 4] which summarize the results of therapy as used by the Renal Insufficiency Center project. In general, the methods consist of: (1) A judicious restriction of fluid intake during the oliguric phase. (2) Administration of calcium ion (as calcium gluconate) to take advantage of the known physiologic antagonism of calcium ion on potassium ion. This therapy is often withheld until the potassium reaches near-critical levels, when beneficial effects may occur promptly and may be fairly lasting (figure 6). Hence valuable time is provided for preparation for artificial dialysis or other procedures. (3) Parenteral therapy for the temporary reduction of serum potassium levels. Such therapy includes (a) the use of sodium ion (as 7.5% $NaHCO_3$ or hypertonic saline), and is of more value if the serum sodium was previously low (figure 5), and (b) the administration of hypertonic (50%) glucose and insulin (figure 4). In the less critically ill patient any or all of the above measures may be sufficient to "hold" the patient until renal function returns, usually after the fourteenth day of oliguria. (4) Artificial dialysis, which is the method of choice when hyperkalemia is severe and maximal benefit has been obtained from the other measures. It is a rapid and most effective method of rearranging the entire ionic pattern of the patient.

Summary

Acute renal insufficiency with subsequent azotemia and hyperkalemia has been observed frequently after extensive war wounding. A severe case is reviewed in detail. Recurrent episodes of potassium intoxication, three of which were interrupted by artificial dialysis, have been closely followed by biochemical determinations and electrocardiographic tracings.

It has been shown that in such a patient the rate of recurrence of potassium elevation is a function of the severity of the trauma, the degree of clinical shock, the amount of tissue necrosis and the degree of subsequent infection. It has been further demonstrated that the electrocardiogram will faithfully record the chemical state of the patient, and that during recurrent hyperkalemia, serial

electrocardiograms will have a similar appearance at comparable chemical levels. Hence the serum potassium level during repeated episodes may be accurately predicted from the electrocardiographic tracing.

The evolution of the electrocardiographic alterations during progressive hyperkalemia has been outlined, and the therapy of such a patient has been briefly discussed.

Summario in Interlingua

In recente annos il ha essite definitivemente establite que in le presentia de persistente oliguria un elevation progressive del concentration de kalium in le fluido extracellular pote devenir directemente responsabile pro le morte del patiente. Le rapiditate con que un tal elevation occurre in le patiente oliguric depende de un numero de circumstantias. In patientes criticamente malade—i.e. in victimas de choc, de vulneres penetrante o contundente, de infection, de reactiones a incompatibile transfusiones de sanguine, o de un combination de iste conditiones—le elevation del concentration de kalium in le fluido extracellular es progressivemente plus rapide in proportion directe al severitate e multiplicitate del complicationes involvite.

Durante le recente guerra corean un considerabile numero de severmente traumatisate soldatos esseva tractate pro uremia e hyperkalemia secundari a acute dysfunctionamento renal. Un del plus informative casos—un caso que exhibi typicamente le procedimentos diagnostic e therapeutic usate—es presentate in detalio. Iste juvene e previemente robuste homine esseva severmente traumatisate e disveloppava subsequentemente quatro distincte e recurrente attaccos de uremia e intoxication a kalium. Tres del attaccos esseva alleviate per medio de hemodialyse artificial. Le quarte attacco esseva mortal.

On ha signalate que le electrocardiogramma es un indispensabile guida del therapia in tal casos, specialmente si illos es characterisate per subitanee e rapide elevationes del concentration del kalium seral. Le curvas electrocardiographic reflecte fidelmente le phenomenos ionic que occurre in le membranas cellular. Consequentemente il es possibile sequer le curso de tal patientes e regular lor tractamento de momento a momento si frequente electrocardiogrammas es executate.

In un specific caso il ha essite demonstrate que le electrocardiogramma reflecte le stato chimic del patiente. Durante recurrente episodios de hyperkalemia, electrocardiogrammas serial exhibi simile configurationes con comparabile concentrationes del electrolytos in le fluido extracellular. Iste facto es illustrate serialmente in le figuras accompaniante le presente articulo.

Durante hyperkalemia il ha plure mesuras therapeutic que pote esser usate pro contra-ager temporarimente le effecto intoxicante del elevate concentration extracellular de kalium. Essentialmente iste mesuras consiste de (1) le utilisation del antagonismo physiologic del ion de kalium (in le forma de gluconato de calcium) contra le ion de kalium o (2) le utilisation del facto que le concentration seral de kalium es temporarimente reducite post le administration de iones de natrium (in le forma de bicarbonato de natrium o de un solution salin hypertonic) o de glucosa hypertonic plus insulina. In le ultime analyse le methodo a preferer in casos de sever hyperkalemia es naturalmente hemodialyse artificial.

BIBLIOGRAPHY

1. Meroney, W. H., and Herndon, R. F.: The management of acute renal insufficiency, J. A. M. A. **155**: 877–883, 1954.
2. Herndon, R. F., Pearson, C. M., and Meroney, W. H.: The electrocardiogram and acute renal insufficiency; a study of hyperkalemia, to be published.

3. Teschan, P. E., Post, R. S., Smith, L. H., Jr., Abernathy, R. S., Davis, J. H., Gray, D. M., Howard, J. M., Johnson, K. E., Klopp, E., Mundy, R. L., O'Meara, M. P., and Rush, B. F.: Post-traumatic renal insufficiency in military casualties; I. Clinical characteristics, Am. J. Med. **18**: 172–186, 1955.
4. Smith, L. H., Jr., Post, R. S., Teschan, P. E., Abernathy, R. S., Davis, J. H., Gray, D. M., Howard, J. M., Johnson, K. E., Klopp, E., Mundy, R. L., O'Meara, M. P., and Rush, B. F.: Post-traumatic renal insufficiency in military casualties; II. Management, use of an artificial kidney, prognosis, Am. J. Med. **18**: 187–198, 1955.
5. Merrill, J. P.: Medical progress; the artificial kidney, New England J. Med. **246**: 17–27, 1952.
6. Taran, L. M., and Szilagyi, N.: The duration of the electrical systole (QT) in acute rheumatic carditis in children, Am. Heart J. **33**: 14, 1947.
7. Winkler, A. W., Hoff, H. E., and Smith, P. K.: Electrocardiographic changes and concentration of potassium in serum following intravenous injection of potassium chloride, Am. J. Physiol. **124**: 478–483, 1938.
8. Merrill, J. P., Levine, H. D., Somerville, W., and Smith, S.: Clinical recognition and treatment of acute potassium intoxication, Ann. Int. Med. **33**: 797–830, 1950.

AN ATYPICAL CASE OF TRICHINOSIS WITH REPORT OF ELECTROMYOGRAPHIC FINDINGS *

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TRICHINOSIS infests about one third of the American people as shown by autopsy studies.[1] It has been estimated to cause 16,000 clinically apparent cases yearly, with a 5% mortality rate.[1] Innumerable clinical patterns appear because symptomatology varies with the number of trichinae ingested, host resistance and sites of dissemination. The classic pattern has been well delineated.[2, 3] The following unusual case is presented to reëmphasize the need for including this entity more frequently in the differential diagnosis of obscure cases, and to describe the electromyographic findings, hitherto unreported in this disease.

CASE REPORT

A 30 year old Negro was admitted to Wadsworth General Hospital on June 6, 1953, complaining of difficult swallowing, weakness of the arms and legs, and profuse diaphoresis of two weeks' duration. His present illness had begun the evening of April 17, when he vomited without apparent cause. The next morning his temperature was 104° F. He entered another hospital, where no etiology for his illness could be determined in spite of extensive diagnostic studies. Laboratory examinations were normal except for an eosinophilia ranging from 7 to 20% on several determinations. His fever persisted, and oxytetracycline was begun 10 days after entry. Within a few days his fever disappeared and he was discharged. He remained well until two weeks before entry to this hospital, when he noted dysphagia without nasal regurgitation, muscular weakness (e.g., he was unable to step up into a streetcar), and excessive sweating. He denied muscular pain or tenderness at any time.

* Received for publication July 6, 1954.
From the Veterans Administration Center, Los Angeles, California.

In response to direct questioning he recalled three days of periorbital edema at the onset of his illness in April, and also remembered helping a friend kill and eat a "home grown" pig shortly before the onset of his illness. He stoutly maintained that the pig was well cooked.

Physical examination on entry disclosed a temperature of 98.6° F., and a regular pulse of 96 beats per minute. The patient was a well developed, fairly well nourished male in no acute distress, moving slowly and walking about somewhat unsteadily.

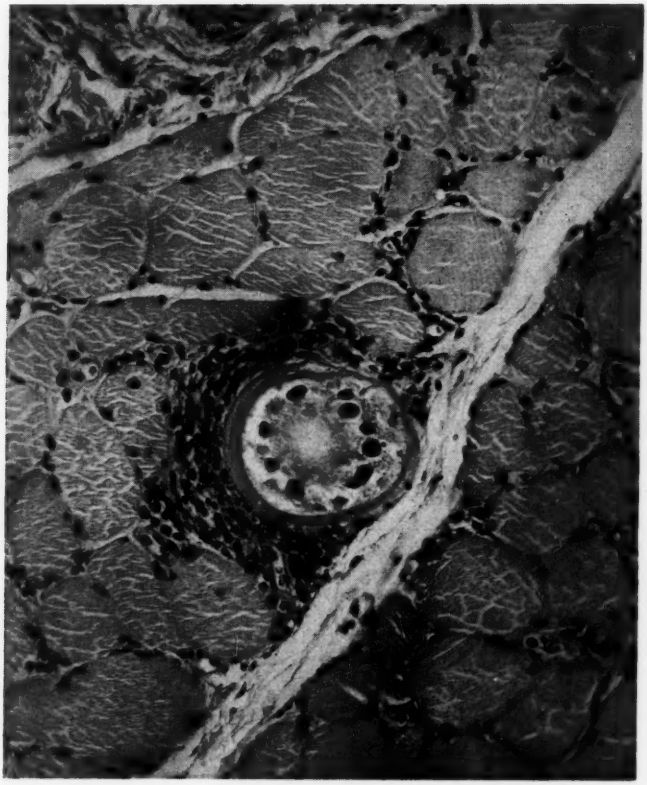

FIG. 1. Trichinosis. Section of biopsy specimen showing the parasite within the muscle.

The cheeks were sunken, and muscle wasting was evident in the temporal, masseter, gluteal and sternocleidomastoid areas. The ability to open the mouth was restricted to half the normal range, and the patient swallowed with great difficulty. Examination of the heart and lungs revealed no abnormalities. The abdominal muscles and the muscles of the extremities, both ventral and dorsal groups, felt exceptionally firm and indurated. He was unable to abduct the arms more than 60°, or to raise the feet more than four to six inches from the ground when standing. There was no

muscle tenderness. All reflexes were present, although decidedly hypoactive and obtainable only after reinforcement. A right Babinski was elicited. Extremity muscle strength was poor in both extensor and flexor groups, while sensation was intact. The rest of the neurologic and physical examination was not remarkable.

Laboratory Data: Examination of the blood on entry revealed 11,400 white cells, with 5% eosinophils, 15 gm. of hemoglobin, a hematocrit of 43 and a sedimentation rate of 18 (Wintrobe). Urinalysis showed a trace of albumin, many red cells and a few white cells per high dry field. The blood cardiolipin test was negative. Spinal fluid examination showed 3 polys, 70 mg. % of sugar, negative Pandy, total protein of 18 mg. %, gold curve of 3321000000, and negative cardiolipin.

Course in Hospital: The initial clinical impression was that the patient had trichinosis; however, a trichinella skin test done soon after entry was negative. Trichinosis was therefore felt to be unlikely. Further studies showed the serum albumin to be 4.1 gm. %, serum globulin, 3.8 gm. %, and normal blood electrolytes. A search for L.E. cells in the peripheral blood was negative. Serum calcium, in-

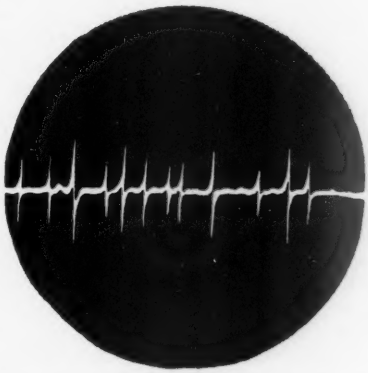

FIG. 2. Electromyogram. Fibrillation voltages at rest. Amplitude 15–20 microvolts, duration 1 millisecond.

organic phosphorus, alkaline phosphatase and fasting blood sugar were within normal limits. Three stool examinations for ova and parasites were negative. An Addis urine count one week after entry showed 24 million red blood cells, 10 million white blood cells and 3.6 million casts. Two initial urine cultures grew out hemolytic *Staphylococcus aureus* and *Proteus vulgaris;* however, four more cultures were negative. Sixteen days after the patient's admission, and on four other occasions, urine examinations revealed no abnormality. An intravenous pyelogram was normal. Subsequent to entry, on six separate occasions the white blood cells ranged from 6,900 to 11,900. Eosinophils were always within normal limits, ranging from 2 to 5%, except once when 12% were present. Routine agglutination tests, reported as negative during his first hospitalization, showed 4 plus 1/160 typhoid O and 2 plus 1/160 typhoid H, 2 plus 1/40 paratyphoid A, 1 plus 1/20 paratyphoid B and negative *Brucella abortus* and proteus OX-19.

An esophagram was reported as showing "disordered motor function of deglutition as seen in bulbar or pseudo-bulbar disease." Because of the marked muscle involvement an electromyogram was done; it showed "the most profuse fibrillation of

denervation this examiner has ever seen" (R. V. M., Jr.). Fibrillation was present in all of the muscle groups examined in the arms and legs. It was interpreted as denoting widespread, severe lower motor neuron pathology. Subsequent electromyograms were done on July 6 and on September 29, and on each occasion there was considerable decrease in the intensity of fibrillation and an increase in normal motor units.

In view of the urinary and neurologic findings a collagen disease was considered. A muscle biopsy was done which disclosed *Trichinella spiralis* (figure 1). A second trichinella skin test was again negative at 10 and 20 minutes and at 24 hours. The patient remained seriously ill. At no time during the hospitalization was he febrile, but the muscular induration, profuse sweating and dysphagia persisted. He lost approximately 20 pounds during the initial period of hospitalization. On June 24 the patient was started on oral cortisone, 100 mg. per day. He seemed to improve slightly, but there was no remarkable change either subjectively or objectively and cortisone was discontinued on July 17. A firm, slightly pitting 2 plus peripheral edema was first noted when cortisone was started. Two electrocardiograms were within normal limits. The edema gradually disappeared in one month. The patient continued to lose weight (approximately 15 pounds more) until July 10, when he weighed 137 pounds. He then gained and by August 10 weighed 146 pounds. 3-o-toloxy-1,2-propane-diol (Tolserol) 1.5 gm. four times daily, was administering during this latter month. Although its administration coincided with the beginning of his improvement, this was probably fortuitous, since the improvement was gradual and continued after Tolserol was discontinued on August 10. The patient received physical therapy throughout most of his hospital course, and this seemed to the patient and physicians to be of definite benefit. The induration of the muscles gradually lessened, and he was able to increase to almost normal the range of motion in the shoulders, hips and knees. The dysphagia also improved, and he was discharged three and one-half months after entry.

In January, 1954, he reported continued improvement. He weighed 165 pounds. A repeat trichinella skin test was positive in 20 minutes. His muscles, especially the peripheral groups, still felt slightly indurated, but swallowing, jaw opening and muscle strength were within normal limits. A right Babinski could still be elicited. The electromyogram showed occasional bursts of fibrillation, especially in the distal muscles, i.e., in the areas of continued muscle hardness (figure 2). The patient was working full time as a bus driver.

Discussion

The classic subdivision of trichinosis into three stages can be demonstrated in the majority of patients with this disease. The intestinal (first) stage usually begins during the second to seventh day after ingestion and corresponds to the liberation of trichinae into the small intestine from digested exogenous muscle. Symptoms and signs of the intestinal stage may be very mild or severe, and are principally those of a nonspecific gastroenteritis.

The second stage, that of muscular invasion, usually begins one week or longer after ingestion and may last five weeks or more. The trichinae liberated in the intestine have matured and reproduced. The resultant offspring invade the intestinal lymphatics, enter the blood stream via the thoracic duct, pass through the pulmonary capillaries to reach the systemic circulation, and are then deposited in striated muscle, where they encyst. The onset of this stage is often characterized by edema of the eyelids, and muscle pain occurs in over 90% of cases.[2, 3]

The third stage, that of convalescence, usually begins five to six weeks from the time of ingestion, and on occasion may last for months. Usually there is complete recovery, but residual difficulties may persist. Death, when it occurs, is most likely between the fourth and sixth weeks.[4]

The time-honored triad of periorbital edema, eosinophilia and muscle tenderness is not present in every case of trichinosis, as is illustrated by the patient reported. Eosinophilia may occur late in the course of the disease, and its early absence is said to presage a poor prognosis.[4] Our patient had a mild eosinophilia at the onset of his illness, only to lose it thereafter, which is also an unusual sequence. Transient periorbital edema, highly characteristic of the state of muscle invasion, is easily forgotten by the patient and may not be recalled unless specifically alluded to. Muscle pain and tenderness, present in a high proportion of cases, was absent in our patient. Possibly the generalized muscle hardness noted in this patient (and in approximately 50% of patients in reported series [3]) may be due to the continuous fibrillation discharges as detected by the electromyogram. Inability to open the mouth, also noted in other patients, has been ascribed to muscle pain, but its presence in our patient excludes a sensory cause.

This patient went through a period of acute illness soon after ingestion of pork, with apparent recovery. Four weeks later he again became severely ill, and gradually became worse during the following two months. The cause of such a diphasic course in trichinosis, which occurs occasionally, is unknown. Primary infection with trichinae is believed to confer increased immunity to reinfection.[3] This patient did not demonstrate skin sensitivity to trichinella extract two months after the onset of his illness. Seven months later the skin test was positive. Whether the initial negativity was merely a delayed reaction, or perhaps corresponded to the anergy seen in overwhelming infection (e.g., tuberculosis) and cachexia, remains conjectural.[5]

At this point it is well to reëmphasize that a positive trichinella skin test merely indicates past, not necessarily recent, infection. The skin test alone cannot be relied upon for diagnosis. On the other hand, the brochure accompanying trichinella extract (Lederle) for skin testing states: "After the usual latent period,* however, a negative trichinella skin test does enable the physician to rule out trichinosis." This case and many others [3] negate this claim. Demonstration of the parasite by biopsy is still the sine qua non and must be done in all suspected cases; of course, a negative muscle biopsy merely rules out trichinella in the piece of the muscle biopsied.

The kidney and neurologic findings are indicative of the extensive dissemination in this case. Decreased to absent tendon reflexes and the presence of the Babinski reflex have been reported previously, and undoubtedly denote widespread nervous system involvement.[6-9] Our electromyograms confirm this. Other organs which have been reported as being involved include the heart (where myocarditis is not at all unusual), lungs, eyes and skin.[3] The differential diagnosis in obscure and atypical cases may therefore require consideration of many of the diseases affecting these organs.

ACTH and cortisone have been reported to be useful therapeutically in trichinosis early in the stage of muscle invasion.[10-14] Cortisone effects were

* Two weeks.

entirely unimpressive in this patient. Perhaps this was due to its use too late in the course of the disease to affect the presumed allergic and toxic manifestations.

It has been established that severe central nervous system damage may result from trichinella infestation. The nervous system changes due to toxins are considered more common and more dangerous than the actual invasion of the parasite.[15] The toxins which cause the degenerative changes in the brain are due to the breakdown products from affected muscles and the catabolic products of the larvae.[16] The marked atrophy of muscles has been attributed to primary invasion of the muscle by the parasites. Most and Ables [6] recognized, however, that some patients presented clear-cut syndromes of involvement of upper and lower motor neurons such as are seen in amyotrophic lateral sclerosis, and concluded that there was anterior horn cell involvement. Our electromyographic findings substantiate severe and widespread lower motor neuron changes. The electromyographic findings also suggest that the severe muscular atrophy and weakness are the result of denervation. It is possible that this is due to a liberated neurotoxin. Electromyographic findings have not been previously reported.

Summary

An unusual case of trichinosis is presented. Trichinella skin tests were negative initially but became positive seven months later. Electromyograms, never before reported to our knowledge in trichinosis, disclosed extensive fibrillation. The significance of these findings is discussed.

We would like to express our appreciation to Dr. Leo Fred and Dr. Leon Rosove for their helpful suggestions.

Summario in Interlingua

Post ingerer carne ab un porco de elevage domestic, un negro de 30 annos de etate disveloppava nausea, transiente edema periorbital e alte temperaturas a maximos acute durante duo septimanas, e transiente eosinophilia. Post tres septimanas additional de apparentemente bon sanitate, ille experientiava sever debilitate muscular, dysphagia, e excessive transpiration sin dolores muscular. Ille se presentava a nos octo septimanas post le declaration de su condition. Alora ille monstrava contabescentia muscular e induration sin dolor sub pression. Le debilitate muscular esseva sever e extense. Le reflexos esseva hypo-active. Un dextere signo de Babinski esseva provocate. Regurgitation nasal non esseva presente. In septe contos differential de leucocytos, eosinophilia esseva observate un vice. Albuminuria e hematuria microscopic esseva initialmente presente sed non se manifestava a plure occasiones ulterior. Duo tests dermatic pro trichinella esseva negative duo menses post le declaration del morbo. Septe menses post le declaration un repetition del mesme test esseva positive in 20 minutas. Un esophagogramma monstrava disordine del function motori de deglutition del typo observate in morbo pseudobulbar. Un electromyogramma monstrava extense fibrillation de denervation. Electromyogrammas, repetite tres o cinque menses post le declaration del morbo, monstrava un considerabile reduction del intensitate del fibrillation. Le diagnose de trichinosis esseva establite per biopsia muscular. Le administration de cortisona in doses de 100 mg per die esseva initiate duo menses post le declaration e continuate durante tres septimanas. Le effecto esseva nil. Patientia e therapia physic pareva le plus importante factores del recuperation.

Trichinosis es subdividite in tres phases: (1) Un phase intestinal con symptomatologia gastroenterologic, (2) un phase de invasion muscular characterisate per edema periorbital e dolores muscular comenciante circa un septimana post ingestion e finiente post cinque septimanas o plus, e (3) un phase de convalescentia comenciante in general cinque o sex septimanas post le ingestion e occupante usque a plure menses.

Le triade de edema periorbital, eosinophilia, e dolor sub pression muscular non es necessarimente presente in omne caso de trichinosis. Edema periorbital escappa a vices al observation si le medico non lo mentiona explicitemente. Eosinophilia pote esser transiente o mesmo absente. Dolores muscular se trova solmente in 90 pro cento del casos.

Nos sublinea que un negative test dermatic pro trichinella non exclude le possibilitate del morbo e que un biopsia muscular es necessari in omne casos de dubita. In le caso presente le transition ab un negative test, duo menses post le declaration, a un positive test, septe menses post le declaration, esseva possibilemente causate per un reaction retardate. Il es etiam possibile que ille facto correspondeva al anergia que es observate in rapide incursiones infectional e in cachexia.

On ha reportate que ACTH e cortisona es therapeuticamente de valor in le prime phases del invasion muscular. In le presente caso le pauco impressionante effecto de cortisona es possibilemente explicabile per le facto que illo esseva administrate nimis tarde in le curso del morbo.

Le generalisate e sever debilitate e induration muscular exhibite per nostre patiente e etiam su dysphagia es explicabile per le constante discargamentos fibrillational que esseva detegibile in le electromyogramma. Iste constatationes indica sever e extense lesiones de inferior neurones motori con ver denervation resultante probabilissimemente ab le action del neurotoxina que esseva producite per le trichinella. In le curso del tempore le anormalitates dispareva, lo que indica un revertibile typo de neuropathia.

Le presente es le prime reporto con constatationes electromyographic in iste morbo.

BIBLIOGRAPHY

1. Editorial, J. A. M. A. **152**: 241 (May 16) 1953.
2. Evans, A. D., and Lennox, M.: An outbreak of trichiniasis in Barry, Glanorgan, Brit. M. J. **2**: 133 (July 18) 1953.
3. Gould, S. E.: Trichinosis, 1945, Charles C Thomas, Springfield, Ill.
4. Conner, L. A.: Atypical clinical forms of trichiniasis, Ann. Int. Med., **3**: 353–359 (Oct.) 1929.
5. Urbach, E., and Gottlieb, P. M.: Allergy, 1946, Grune and Stratton, New York, pp. 23–24.
6. Most, H., and Ables, M. V.: Trichiniasis involving the nervous system, Arch. Neurol. and Psychiat. **37**: 589–616 (Mar.) 1937.
7. Scott, A., Johnson, R. E., and Holyman, D.: Trichinosis, with neurologic and mental manifestations, New England J. Med. **247**: 512–514 (Oct. 21) 1952.
8. Skinner, J. C.: Neurologic complications of trichinosis, New England J. Med. **238**: 317–319 (Mar. 4) 1948.
9. Merritt, H. H., and Rosenbaum, M.: Involvement of the nervous system in trichiniasis, J. A. M. A. **105**: 1646–1649 (May 9) 1936.
10. Solomon, C., and Seligman, B.: Response of trichiniasis to adrenocorticotropic hormone (ACTH) therapy, New York State J. Med. **52**: 1444–1446 (June) 1952.
11. Rosen, E.: Cortisone treatment of trichinosis, Am. J. M. Sc. **233**: 16 (Jan. 9) 1952.
12. Davis, W. M., and Most, H.: Trichinosis, case report with observation of the effect of adrenocorticotropic hormone, Am. J. Med. **11**: 639–644 (Nov.) 1951.

13. Luongo, M. A., Reid, D. H., and Weiss, W. A.: The effect of ACTH in trichinosis, New England J. Med. **245**: 757–760 (Nov. 15) 1951.
14. Buylla, P. A., Llavona, V. A., and Villarroya, P. F.: Outbreak of trichinosis treated with ACTH, Rev. clín. españ. **49**: 151–218 (May 15) 1953; abstracted J. A. M. A. **153**: 690 (Oct. 17) 1953.
15. Evers, L. B.: Manifestations of trichiniasis in the central nervous system, Arch. Int. Med. **63**: 949–956 (May) 1939.
16. Hassin, G. B., and Diamond, I. B.: Trichinosis encephalitis: a pathologic study, Arch. Neurol. and Psychiat. **15**: 34–47 (Jan.) 1926.

TREATMENT OF A CASE OF RELAPSING PANNICULITIS WITH CORTISONE AND ACTH *

By Stanley Crosbie, M.D., *Grand Junction, Colorado*

Although the clinical-pathologic features of this syndrome are said to have been described by Flemming in 1872 and by Pfeiffer in 1892, the disease takes its proper name from Weber,[1] who published his paper in 1925, and from Christian,[2] whose paper in 1928 added the word "febrile" to its descriptive title. The first case reported in this country was by Gilchrist and Ketron[14] in 1916 under the title, "A Unique Case of Atrophy of the Fatty Layer of the Skin Preceded by the Ingestion of the Fat by Large Phagocytic Cells—Macrophages."

Shuman[3] reviewed the literature in his paper published in 1951 and reported a total of 54 cases, including one of his own.

The pathology lies in the panniculus adiposus, not in the dermis. The most striking microscopic feature is the formation of irregular masses of fat. There are edema and necrosis of the fat cells, which appear to be followed by phagocytosis of the fat droplets by macrophages. There is lymphocytic infiltration all around the fat cells, with occasional plasma and connective tissue cells but very few granulocytes. Multinuclear giant cells, formed perhaps from macrophages, are seen. Occasionally small arterioles running through this area will show some proliferation of the endothelium.

The nodules vary in size from a few millimeters to several centimeters. Shuman's case[3] had a mass 28 by 8 cm. in the right flank. Most often the nodules vary from 1 to 3 cm. in diameter, and are most common on the extremities and trunk. Rarely are they found on the face, palms of the hands or soles of the feet. They are usually slightly raised over the surrounding uninvolved skin and quite red when they first appear, changing to a light purple as they begin to fade. Usually they are not particularly tender to superficial palpation, but deep pressure may cause discomfort. The skin over the nodule is apt to feel thickened, and one gets the impression in palpating the lesion that there is a small mass just below the epidermis which moves rather freely. A dimpling of the center of the nodule is described by some authors as the lesion begins to regress, but it was not observed in this case. Multiple nodules are the rule, but some cases show only a few with each attack. As the lesions

* Received for publication August 2, 1954.

fade they are apt to leave a dirty brownish pigmentation which may remain for some time. Frequently, but apparently not invariably, there is a depression left at the site of the nodule after it has resolved, due probably to the fat necrosis and atrophy of the involved area.

Although the pathology usually involves the skin or, more precisely, the panniculus adiposus just beneath the dermis, there are reports of involvement of adipose tissue elsewhere in the body, as, for example, in the pericardial, epicardial, perirenal, peritoneal, peripancreatic and omental adipose tissue. In the case reported by Spain and Foley,[10] nodules were found in mesenteric, omental and pretracheal fat deposits.

The clinical picture is extremely variable, and without the characteristic nodules a diagnosis of relapsing panniculitis would be extremely difficult. Sometimes the nodules appear before the systemic symptoms and disturb the patient very little. Again, as in the case reported here, prodromal symptoms may precede the appearance of the characteristic nodules by weeks or months.

About three quarters of the cases reported have been in women, and the condition may occur at almost any age except in very young infants. Systemic symptoms mentioned by various authors include muscle pains or joint symptoms, weakness, malaise, nonproductive cough, nausea and vomiting, headache, chills and a fever which may be either septic or undulating. The highest fever recorded in the case reported here was 105° F. The fever may persist for weeks or months. In the present case fever lasted for about six weeks prior to and during his first hospital admission before there was a spontaneous remission. During his second admission fever was prominent for two months before it returned to normal coincident with the administration of ACTH.

However, as pointed out by Friedenberg,[4] fever is not an integral part of the disease, and his two cases as well as at least five others reported in the literature showed little or no rise of temperature.

As the name implies, remissions and exacerbations are the rule. This patient has probably had at least three major attacks of the disease and as many minor episodes, which appear to have been aborted by the steroids, in something over three years.

Shuman's case [3] showed very definite and progressive neurologic signs, including ataxia, motor and sensory loss and certain reflex changes. Since no autopsy was performed, it would be impossible to say whether this was due to the disease under consideration or to some other central nervous system lesion.

Reports on the effectiveness of treatment with cortisone and/or ACTH have been varied, some good, some poor and some indifferent. Friedenberg [4] gave his female patient cortisone for a period of one week, with no benefit and possibly some delay in healing of a biopsy site. His second case was apparently not treated with cortisone or ACTH. Shuman's case received cortisone for eight days before there was any noticeable effect. The medication caused no alteration in the size of the nodules, and Shuman seems to feel that the drop in temperature was a fairly nonspecific effect. Terminally, ACTH was used in the same case with no obvious benefit.

The case reported by Doerner, Naegele, Regan and Cameron [5] received full cortisone therapy, but although there was marked subjective improvement in the

sense of well being and appetite there appeared to be no influence on the course of the fever or the joint pains.

Case Report

First Admission: This 60 year old farmer was first admitted to the Veterans Administration Hospital in Grand Junction, Colorado on November 8, 1950, complaining of chills, fever, anorexia and generalized muscle pain for about six weeks prior to admission. Before that he had been entirely well. He first noted pain in the muscles of the thighs, but within 24 hours most of the muscles were painful and tender. He gave no history of joint symptoms, but stated that he had had episodes of chills and fever prior to admission. Anorexia had been present throughout this period, resulting in a 20-pound weight loss. There was no nausea or vomiting. Weakness and ease of fatigue had been prominent.

The family history did not appear significant.

The patient's past history revealed an attack of fever and calf pain diagnosed as inflammatory rheumatism at the age of 22 years. However, this illness lasted only a week and there were no joint symptoms.

The positive physical findings at the time of this first admission included a Grade II attenuation of the retinal arterioles, with moderate sclerosis and tortuosity. There were also noted a Grade II apical systolic murmur, left varicocele and internal hemorrhoids.

Laboratory studies yielded a white blood cell count of 5,350, with 33% segmented and 33% band form neutrophils, 32% lymphocytes and 2 monocytes. Hemoglobin, 12 gm.; hematocrit, 39%; sedimentation rate, 51 mm. per hour corrected to 36. The neutrophils showed heavy toxic granulations. Urinalysis, chest x-ray and electrocardiogram were essentially negative, as were numerous other laboratory tests.

The patient spiked a fever as high as 102° F. for five days but then became afebrile without medication and was sent out on a convalescent leave for two weeks. On his return he was asymptomatic, had gained 10 pounds in weight, and had a normal white blood cell count and differential, with a hematocrit of 43% but still a slightly elevated sedimentation rate (36 mm.).

He was discharged on December 8 with a diagnosis of fever of undetermined origin.

Second Admission: The patient was again admitted to the same hospital on February 27, 1951, complaining of weakness, anorexia, weight loss and painful muscles. He stated that he had remained well for two to three weeks after his previous hospitalization but then again developed pain in the calf muscles, followed by transient migratory pain in other muscle groups. There was no history of trauma.

Physical examination disclosed some evidence of recent weight loss but was not significantly different from the first examination except that on both arms there were several slightly raised, reddish, indurated areas measuring about 1 cm. in diameter. They appeared to be intradermal or just subdermal and were not particularly tender. They did not itch.

The hemogram at the time of this second admission showed a white blood cell count of 10,600, with 41% segmented and 26 band form neutrophils, 31% lymphocytes and 2 monocytes. Hemoglobin, 9.5 gm.; hematocrit, 31%. Uncorrected sedimentation rate, 55 mm., corrected to 30. There were marked toxic granulation, moderate anisocytosis, poikilocytosis and polychromasia. The following studies were negative or within normal limits: urinalysis, serology, agglutination for typhoid, paratyphoid, brucella and proteus OX-19, stools for blood and parasites, blood, urine and stool cultures, bleeding and coagulation time. The spinal fluid pressure and dynamics were

normal, and examination of the fluid disclosed 3 cells with a total protein of 36 mg.%, which is at the upper limit of normal for this laboratory. The complement fixation and gold curve on the spinal fluid were negative. The thymol turbidity was 13 units; total serum protein, 7.9 gm., with 3.3 gm. of albumin and 4.6 gm. of globulin. Icterus index, 3 units; blood urea nitrogen, 11 mg.%. The acid phosphatase measured 0.6 unit and alkaline phosphatase, 9.2 units (Gutman). Cephalin flocculation, 4 plus. Bromsulphalein, 11% retention at 45 minutes.

Sputum cultures grew some common nonspecific organisms. Malaria smears were negative. Fasting blood sugar, 115 mg.%; serum chlorides as NaCl, 561 mg.%. An examination for L.E. cells was negative.

Chest x-ray showed nothing but slight hilar accentuation. Gastrointestinal and colon series were negative. X-ray of the hands revealed some vascular calcification. Skin tests with trichinella antigen and coccidioidin were negative, as was the skin test with PPD.

The patient's temperature curve was of the septic type, with daily spikes as high as 103° F. from the time of admission until April 25. Chloromycetin and Terramycin, as well as numerous other medications, seemed to have little effect on the temperature or well being of the patient. He lost 11 pounds.

On April 24 1951, intramuscular ACTH was started, with an initial dose of 60 mg. daily, divided into four equal parts. Whereas the patient's temperature chart had shown almost daily spikes of fever of from 101° to 103° F., with a rise to 105.6° F. on the day before therapy was started, the temperature fell to a subnormal level within three hours after the first dose of 15 mg. of ACTH. The temperature remained normal or below for almost two weeks as the dosage of ACTH was gradually reduced to 48, 40 and 30 mg. daily. The patient's sense of well being increased. On this dosage (30 mg. daily) there was a slight rise of fever (to about 100° F.) for three days, but when the dosage was further reduced (to 15 mg. of ACTH daily) the temperature remained normal for five days and then rose to slightly over 100° F. ACTH was discontinued for two days and the temperature promptly rose to 101° F. Several new nodules appeared and the subjective symptoms returned. With 30 mg. of ACTH the temperature fell to normal again and the patient was relieved of his symptoms. The raised, slightly tender nodules faded and disappeared. Fifteen milligrams of ACTH daily for six days failed to maintain the well being, and the temperature rose to 101° F.

On June 3 the route of administration of the ACTH was changed from intramuscular to intravenous. Fifteen milligrams were put into 500 c.c. of 5% glucose solution and given by slow drip over an eight-hour period. The patient was well maintained on 15, then 12, and then 10 mg. of ACTH daily. He was then allowed to go home for three days without medication. He returned with a temperature of 104° F., great malaise, pains in the arms and legs, and several new nodules on the arms. ACTH was again effective. Ten days later discontinuance of ACTH for four days caused an even more marked exacerbation—fever to 104° F., muscle pains and numerous circumscribed scarlatinal areas of from 1 mm. to 4 cm. in diameter, some of which were raised. They were only slightly tender and did not itch. They occurred on the upper extremities, chest, neck, groin and upper thighs.

With this exacerbation it was decided to try cortisone, starting with 300 mg. daily in divided doses given intramuscularly. The effect of this drug was not so dramatic as that of ACTH, but definite improvement was noted within 24 hours, and within three days the nodules were fading and the temperature was normal. Cortisone dosage was reduced to 200 mg. the second day and 100 the third. Oral cortisone, starting with 75 mg. three times a day, was substituted and was just as effective. Two days later this dosage was reduced to 50 mg. three times a day, and then in another six days to 125 mg. daily in divided doses. There was no re-

currence of either symptoms or signs, so the oral cortisone was reduced to 100 mg. daily and then to 75 mg. This latter dosage, however, failed to maintain his well being, so the 100 mg. daily dosage was again instituted, with subsidence of the symptoms. However, fluid retention developed, requiring a lower sodium intake.

On August 29 the patient was allowed to leave the hospital on a two-day pass. He returned with fever and several nodules on the upper extremities. He was given 15 mg. of ACTH by slow intravenous drip.

No further ACTH or cortisone was required during this admission. By September 10 the patient was asymptomatic and was allowed to return home on a 10-day leave. He returned in good condition and was discharged on September 20, 1951.

A biopsy of one of the nodules was taken on May 25. The section shown in figure 1 is believed to be consistent with a diagnosis of nodular, nonsuppurative,

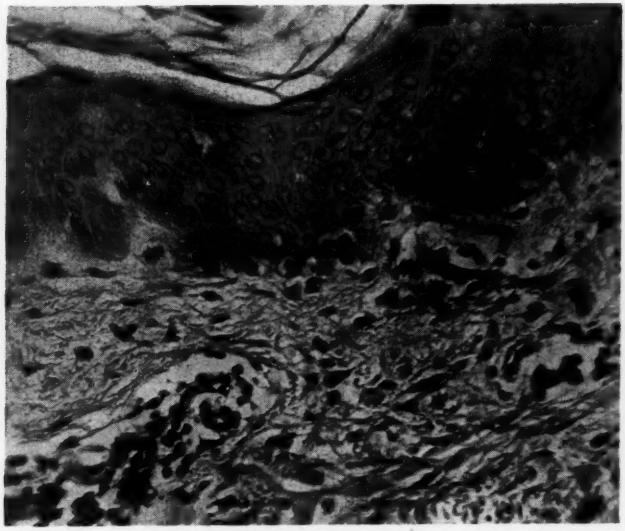

FIG. 1. High power photomicrograph taken from the case presented, showing perivascular round cell infiltration in the dermis.

relapsing panniculitis. Cultures of biopsy material showed no growth of bacteria or fungi.

Third Admission: The patient was admitted again on September 2, 1952. However, this admission was principally for treatment of an infected ingrown toenail, and there was no evidence of the relapsing panniculitis, although he stated that he occasionally noted pain in the lower extremities and sometimes in other muscle groups.

Fourth Admission: On December 1, 1952 the patient was admitted to determine eligibility for nonservice-connected compensation. He had had no acute flare-up of the panniculitis since September, 1951, but had continued to suffer from muscle pain, especially in the lower extremities. He had been able to work for only short periods each day. The pain was of two types: one a stinging sensation in the skin quite similar to that he had had prior to the development of the cutaneous nodules,

the other described as a muscle soreness aggravated by movement and most persistent in the lower extremities but also felt in the hands, shoulders and back.

Although it was believed that these symptoms might represent residuals of relapsing panniculitis or a subclinical form of the disease, there was sufficient evidence for a diagnosis of arteriosclerosis obliterans, and the patient was discharged with this diagnosis.

Fifth Admission: On May 22, 1953, the patient was admitted for the fifth time with the following complaints: (1) generalized weakness and malaise of two weeks' duration; (2) aching pain in the right leg; (3) raised, reddened, tender nodule on right forearm.

The patient stated that although he had had some muscle pain, especially in the legs, off and on, in general he had been fairly comfortable and able to work most

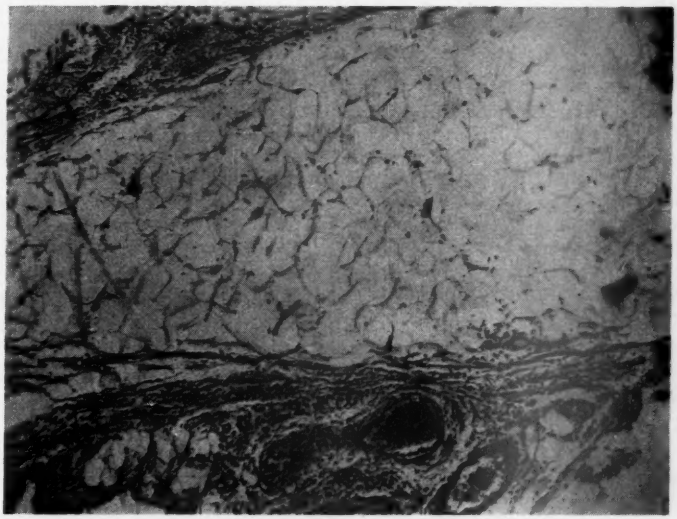

FIG. 2. High power photomicrograph of a section through the panniculus adiposus, showing edema and necrosis of fat cells with macrophages and lymphocytic infiltration. Taken from the case presented.

of the time since his previous admission. However, about two weeks prior to this admission he had developed weakness and malaise without any apparent antecedent cause. Within a few days nodules appeared on the upper extremities similar to the ones noted previously but somewhat more tender. He had noted five or six such nodules, but at the time of admission there was only one, on the right forearm.

Physical examination at this time was essentially unchanged as compared with the previous examination. The patient was febrile and there was a 1.5 cm. red, slightly indurated and somewhat tender nodule on the volar surface of the right forearm. There was a small red spot about the same size just above the olecranon process on the same side, but this spot was not raised, indurated or tender. A third spot, also on the volar surface of this forearm, was pigmented but not red, raised or tender.

Laboratory studies revealed a white blood cell count of 6,400, with 71% segmented and 3 band form neutrophils, 22% lymphocytes, 3% monocytes and 1 eosinophil. Hemoglobin, 14.8 gm.; hematocrit, 45%. The erythrocyte sedimentation rate was 50 mm. per hour uncorrected. Chest x-ray and urinalysis were essentially negative. Electrocardiogram and other studies were normal or negative.

The patient was not immediately started on the steroids, to see if the symptoms would subside spontaneously. The first day the temperature rose to 101° F., the second day to 101.4° F., and the third day to 102° F. Codeine and aspirin failed to control the leg pain or headache. Weakness and malaise increased.

On the fourth hospital day the patient was started on ACTH. Twenty milligrams were given slowly intravenously in 500 c.c. of 5% glucose. Within less than one hour after the ACTH was started the patient noted some relief of the pain in his legs, and within 24 hours the temperature was normal. A second 20 mg. of ACTH were given the following day, and then oral cortisone was substituted in a dosage of 25 mg. twice a day. For the next six weeks the patient required either cortisone or ACTH to control his symptoms, and when one of the two was not used daily an exacerbation resulted.

In the middle of July, 1953, the patient was sent out on a two weeks' furlough with instructions to continue oral cortisone, 50 mg. daily. He remained asymptomatic and on his return was given a month's furlough on the same dosage. This was followed by another month's leave on cortisone. On his return he was feeling so well that it was decided to discharge him without medication.

Subsequent Course: This patient has been followed periodically since his discharge in September, 1953. He has remained well, for the most part, without regular doses of cortisone. Several times he has noted a recurrence of the pain in his legs and some weakness and malaise. Each time his local physician has given him cortisone for a few days, with complete disappearance of his symptoms. The patient is apparently well and is again able to do most of the work on his farm.

Discussion

The list of suggested etiologic factors in Weber-Christian disease is as long and as varied as in other diseases of obscure origin. Weber[1] suggested that the use of bromides and iodides might be an etiologic factor in this disease, and others reporting cases later believed they noted some relationship.

Trauma has been stressed by Binkley,[6] and the onset of the disease in Shuman's case [3] appeared to be related to an injury.

A vitamin deficiency was suspected in the case presented by Tilden, Gotshalk and Avakian,[7] but spontaneous remission is so common in this disease that the response of their patient to correction of dietary deficiency may have been fortuitous.

Impaired fat metabolism, endocrine disease, renal failure and many other pathologic conditions have been linked with Weber-Christian disease.

In reading over case histories, however, one is impressed by the number of cases which seem to be related, directly or indirectly, to infection, focal or generalized, or to diseases such a arthritis, which some investigators have thought might be related to infectious agents through an antigen-antibody response. Binkley [6] noted the association of dental and tonsillar infection as well as arthritis with panniculitis. All five of Bailey's [8] cases had tonsillar and dental infection, and one had rheumatism. Brudno's case [9] had a family history of rheumatoid arthritis, and the patient had a 14-year history of rheumatic disease as well as drug sensitivity. Weber [1] himself suggested a relationship to

rheumatism in his original paper in 1925, and his case had had "rheumatic pains all over her body." The case reported by Doerner, Naegele, Regan and Cameron [5] died of tuberculous meningitis within a few months of an episode of panniculitis, and the case of Tilden, Gotshalk and Avakian [7] died of tuberculosis within less than a year after a typical attack of panniculitis. Spain and Foley [10] noted the association of panniculitis and chronic glomerulonephritis in their case who died of uremia.

Numerous other examples of a possible association with infection are found in the literature but, with one possible exception, attempts to culture bacteria from the nodules themselves have been unsuccessful.

The possibility of bacterial allergy as the precipitating factor in Weber-Christian disease has been suggested many times in the past. In 1946 Duran-Reynals [11] published a very interesting study describing how necrosis of fat tissue could be produced in several different breeds of rabbits at the Rockefeller Institute. These rabbits were found to have small hemorrhages in the fat and muscles, particularly in a pad of abdominal fat extending from groin to perirenal region along the psoas muscles. If these animals were injected intravenously, intradermally or intratesticularly with any one of a wide variety of materials such as Brown-Pearce tumor, the Shope fibroma, virus III of rabbits, vaccinia, avian tuberculosis, hemolytic streptococci, anthrax, *Escherichia coli* and testicular or other tissue extracts, they developed palpable masses of the abdominal cavity in a few days. Histologic examination of these nodules revealed fat necrosis, the infiltration of cells of various sorts, phagocytosis of fat droplets by macrophages, the formation of giant cells and, finally, fibrosis similar in many respects to the lesions of Weber-Christian disease. It was apparently not necessary to sensitize these animals first to these foreign substances. Not all of the animals so injected developed the nodules, and a few developed them spontaneously without injection of foreign materials. Extracts and filtrates of these nodules when injected into control rabbits appeared to be the most effective way of producing the typical lesions. Duran-Reynals believed that the condition occurred in epidemic-like form in 1932–1934. He also noted that tests done in a "contaminated" environment were more successful than those carried out in a "clean" environment. Because of this, and because he was unable to culture any bacterial agent, he suspected a viral etiology. While such a conclusion is reasonable, an allergic reaction in animals with a native or acquired sensitivity would also seem possible.

Bendel,[12] after a careful review of the literature, suggests that the mechanism of relapsing panniculitis may be a nonspecific type of allergy. Johnson and Plice [13] suggest bacterial allergy as an etiologic factor. Brudno [9] theorizes about an antigen-antibody reaction resulting in destruction of the cell membrane with the liberation of free fat. Friedenberg [4] concludes that an allergic systemic reaction is a reasonable explanation of this disease.

It is believed that the dramatic response to ACTH and cortisone in the case presented is another small piece of evidence suggesting that Weber-Christian disease is in some way related to an antigen-antibody response. In view of the wide variety of precipitating factors which have been cited in other cases, the inconstant clinical picture, the uncertainty in prognosis and the difference in response to various methods of treatment, particularly the steroids, it seems reasonable to suppose that this antigen-antibody response is not specific but

may be called out by a number of factors, not only bacterial and viral but possibly chemical. In the case presented it is suggested that the illness which prompted his first admission was not an attack of relapsing panniculitis (sine panniculi) but a bacterial (or viral) infection which we were not able to localize, and that the attack of panniculitis which followed in about three months was a result of the previous sensitization. The fact that all cases of Weber-Christian disease do not appear to respond to ACTH or cortisone does not seem to invalidate this hypothesis, since the same variation in clinical response is seen in other disease syndromes believed to be due to the antigen-antibody response.

Summary

A case of relapsing, febrile, nodular, nonsuppurative panniculitis is presented. Treatment with ACTH or cortisone during two major and several minor attacks appeared to result in a dramatic response, with fall in temperature, disappearance of nodules, relief of muscle and joint pain and return of a sense of well being. It is the author's opinion that this response may be further evidence of an antigen-antibody type of reaction as the etiologic factor in Weber-Christian disease.

Summario in Interlingua

Ben que le recognition clinico-pathologic de iste syndrome es le merito de Flemming e data de 1872, le morbo es nominate pro Weber qui publicava su articulo super illo in 1925 e Christian qui addeva le termino "febril" in 1928.

Le pathologia jace in le panniculo adipose e consiste de massas irregular de grassia, necrosis de grassia, e phagocytosis de guttulas de grassia per macrophagos.

Le nodulos varia in dimensiones ab alicun millimetros a plure centimetros—rarmente plus. Illos occurre le plus frequentemente in le extremitates. Illos es usualmente elevate, rubie, e non sensibile sub pression e regrede intra dies o septimanas. Pigmentation o leve depressiones remane frequentemente in le loco del nodulos.

Le aspectos clinic del morbo non es constante. Nodulos precede o seque le manifestationes systemic. Istos pote includer dolores muscular o arthralgia, malaise, tusse, nausea, vomito, migraine, frigido, e febre. Exacerbationes e remissiones es le norma.

Circa 60 casos es reportate in le litteratura, tres quartos in feminas. Omne etates es involvite, excepte illo del neonatos.

Le problema del therapia remane sin solution satisfactori. In alicun casos effectos benefic esseva obtenite per corticoides e corticotrophina.

Es presentate le caso de un fermero de 60 annos de etate. Ille esseva hospitalisate al Hospital del Administration de Veteranos a Grand Junction in Colorado in 1950. Su symptomas includeva frigido, febre, anorexia, perdita de peso, e dolores muscular.

Studios extense non succedeva a clarificar le etiologia de su caso. Ille recuperava intra un mense sin tractamento specific.

Ille esseva rehospitalisate duo menses plus tarde con le mesme symptomas. Le examine physic non esseva remarcabile, excepte que plure levemente elevate e indurate nodulos rubie esseva constatate al superficie de su bracios.

Varie antibioticos non influentiava le febre septic que attingeva maximos de plus que 40 C. Post duo menses, un curso intramuscular de 60 mg ACTH per die esseva initiate. Le temperatura se abassava a un nivello normal intra tres horas e remaneva normal quando le dose de ACTH esseva reducite. Quando le dose esseva cambiate a 10 mg per die, date per administration intravenose, le patiente se monstrava ben mantenite. Cortisona esseva substituite pro ACTH, sed pro obtener le mesme mantenentia un dose de 100 mg per die esseva requirite. Le interruption del tractamento resultava in un augmento del febre e del nodulation.

Post quatro menses le administration del steroides esseva reducite e tunc cessate. Le patiente remaneva sub observation durante duo annos. Nulle nodulation occurreva, sed Cortona® esseva administrate plure vices per le medico de familia quando se re-presentava signos premonitori de malaise e dolores muscular.

In 1953 un hospitalisation final esseva requirite a causa de simile symptomas accompaniate de nodulation. Antibioticos resultava in nulle responsa, sed le responsa a corticotrophina esseva dramatic.

Ab ille tempore le patiente ha remanite in bon stato de valetude ben que ille ha requirite sporadic administrationes de cortisona.

Le etiologia del morbo non es cognoscite. Le theorias que ha essite avantiate incrimina bromidos, iodidos, trauma, carentia vitaminic, defectos del metabolismo de grassia, disequilibrio endocrin, dysfunctionamento renal, infection, e rheumatismo. Allergia viral esseva proponite in 1946 per Duran-Reynalds qui demonstrava un simile pathologia in conilios ubi le condition occurre in formas quasi-epidemic e pare esser relationate de maniera inconstante con le injection de varie substantias estranie.

Altere autores opina que iste morbo es connectite in un maniera o un altere con un reaction de antigeno e anticorpore. In le caso del presente reporto le responsa dramatic a corticotrophina e Cortona® es considerate per nos como supporto del ultimo-mentionate etiologia.

BIBLIOGRAPHY

1. Weber, F. P.: A case of relapsing non-suppurative nodular panniculitis showing phagocytoses of subcutaneous fat cells by macrophages, Brit J. Dermat. **37**: 301–311, 1925.
2. Christian, H. A.: Relapsing, febrile, nodular, non-suppurative panniculitis, Arch. Int. Med. **42**: 338–351, 1928.
3. Shuman, C. R.: Relapsing panniculitis (Weber-Christian disease), Arch. Int. Med. **87**: 669–681, 1951.
4. Friedenberg, R.: Weber-Christian disease. A report of two cases, Ann. Int. Med. **38**: 528–532, 1953.
5. Doerner, A. A., Naegele, C. F., Regan, F. D., and Cameron, G. F.: The development of tuberculous meningitis following cortisone therapy, Am. Rev. Tuberc. **64**: 564–571, 1951.
6. Binkley, J. S.: Relapsing, febrile, nodular, non-suppurative panniculitis, report of a case, J. A. M. A. **113**: 113–116, 1939.
7. Tilden, I. L., Gotshalk, H. C., and Avakian, E. V.: Relapsing, febrile, non-suppurative panniculitis, Arch. Dermat. and Syph. **41**: 681–689, 1940.
8. Bailey, R. J.: Relapsing, febrile, nodular, non-suppurative panniculitis (Weber-Christian disease), J. A. M. A. **109**: 1419–1425, 1937.
9. Brudno, J. C.: Chronic, febrile, nodular, non-suppurative panniculitis (Weber-Christian disease). Relation to rheumatic fever and allied diseases, J. A. M. A. **243**: 513–517, 1950.
10. Spain, D. M., and Foley, J. M.: Non-suppurative, nodular panniculitis (Weber-Christian disease), Am. J. Path. **20**: 783–787, 1944.
11. Duran-Reynals, F.: Necrotizing disease in rabbits affecting fatty and muscular tissues: analogies with Weber-Christian disease in humans, Yale J. Biol. and Med. **18**: 583–594, 1946.
12. Bendel, W. L., Jr.: Relapsing, febrile, nodular panniculitis (Weber-Christian disease), Arch. Dermat. and Syph. **60**: 570–596, 1949.
13. Johnson, W. A., and Plice, S. G.: Relapsing febrile nodular nonsuppurative panniculitis: report of case with review of literature, Arch. Path. **48**: 281–286, 1949.
14. Gilchrist, T. C., and Ketron, L. W.: A unique case of atrophy of the fatty layer of the skin preceded by the ingestion of the fat by large phagocytic cells—macrophages, Bull. Johns Hopkins Hosp. **27**: 291, 1916.

EDITORIAL

RESERPINE IN THE TREATMENT OF NEUROPSYCHIATRIC DISORDERS

Rauwolfia serpentina in the form of crude pharmacologic preparations seems to have had an important place in the folk-lore medicine of India for many years as a reputed cure for "insanity" and many other ills. More recently better documented reports of its use have appeared in Indian medical journals, most of which are not readily accessible in this country. These are now chiefly of historical interest, although they doubtless served as a stimulus to serious scientific investigation of the preparation. This study was greatly intensified following the isolation of the principal alkaloid, reserpine, by Miller, Schlittler and Bein [1] in the Ciba laboratories in 1952.

Since then reserpine has been studied extensively from the pharmacological and clinical standpoints both in Europe (especially Switzerland) and in this country. Experiments to determine its mode of action on the nervous system are too detailed for discussion here and not yet conclusive. The major effects of reserpine, however, appear to depend upon the inhibition of sympathetic impulses arising in the hypothalamic region of the midbrain.[2] Although the parasympathetic system apparently is not directly affected by reserpine, the net result is a parasympathetic preponderance which accounts for many of the undesired "side effects" as well as its primary activity. Although reserpine may potentiate the effects of hypnotics and other depressants, its manner and sphere of activity are quite different. It does not directly depress the cerebral cortex and cause mental confusion and sleep like the barbiturates, as shown by clinical observations and by an "alert" type of electroencephalogram. Neither does it cause ataxia or any notable disturbance of muscular activity.

The earlier clinical studies were confined primarily to hypertensive subjects, but the quieting effect noted in some of the tense emotionally disturbed patients in this group led rapidly to a trial in subjects with similar disturbances but with normal blood pressure. This movement undoubtedly was greatly stimulated by the exhibition of the strikingly "tranquilized" monkeys during the annual session of the American Medical Association at San Francisco in 1954, and by the illustrations of these animals in widely circulated advertisements. If it will so tame a savage beast, why not a man? In any case, the use of reserpine (as well as chlorpromazine or both in combination) has caused a minor revolution in the therapeutic procedures of many of the large mental hospitals throughout the country, particularly in the management of the most intractable and violently dis-

[1] Miller, J. M., Schlittler, E., and Bein, H. J.: Reserpin, der sedative Wirkstoff aus Rauwolfia Serpentina Benth, Experentia **8**: 338, 1952.

[2] Bein, H. J.: Significance of selected central mechanisms for the analysis of the action of reserpine, Ann. New York Acad. Sc. **61**: 4–16, 1955.

turbed patients. A year is far too short a time to warrant any opinion as to late results, but the large number of cases treated, already running into thousands, does warrant some tentative conclusions as to immediate and "short term" results.

Much of this work was reported or reviewed at a Conference held by the Section of Biology of the New York Academy of Science, Feb. 3 and 4, 1955, and recently published in their Annals.[3] It is necessary to distinguish sharply between results obtained in the severe psychoses, usually requiring massive doses, and in the ordinary psychoneuroses in which as a rule only small doses are well tolerated. It is with the first group that the most definite information is available.

The earliest reported study in this country of the use of reserpine in psychotic patients was that of Kline[4] who obtained encouraging results which were statistically significant in a series of 411 cases with a dose which was grossly inadequate according to present standards. Subsequent observations with more adequate doses have since been published[5, 6] and will furnish much of the basis for this review as they are representative of the more successful studies reported by other observers. Their most detailed report concerns 200 psychotic female patients selected because of "their excited, hyperactive, assaultive or destructive behavior," and a few subjects in profound stupor. Of these, 159 were classed as schizophrenic, 150 had been subjected to insulin coma or electroshock treatments (EST), 55 were receiving maintenance shock treatments once or twice a week, and 14 had had cerebral operations (leukotomies) of some type. Large doses were given and adjusted to the needs of the individual, if necessary increased into the massive range. A combination of oral and intramuscular administration was found most effective.

Patients who responded favorably usually showed some improvement within a week (occasionally much later), in that they became quieter, less disturbed, often drowsy—the "sedative period." Frequently they then passed through a "turbulent period" of increased restlessness, agitation, tension, anxiety, with even more disturbing delusions and hallucinations.[5, 7, 8] If intensive treatment is continued, in favorable cases this subsides after a few days or weeks and is followed by an "integrative period" in which the

[3] Miner, R. W. (editor): Reserpine in the treatment of neuropsychiatric, neurological, and related clinical problems, Ann. New York Acad. Sc. **61**: 1–280, 1955. (Conference report.)

[4] Kline, N. S.: Use of *Rauwolfia serpentina* Benth in neuropsychiatric conditions, Ann. New York Acad. Sc. **59**: 107, 1954.

[5] Kline, N. S., and Stanley, A. M.: Use of reserpine in a neuropsychiatric hospital, Ann. New York Acad. Sc. **61**: 85–91, 1955.

[6] Barsa, J. A., and Kline, N. S.: Treatment of two hundred disturbed psychotics with reserpine, J. A. M. A. **158**: 110–113, 1955.

[7] Sainz, A. A.: The use of reserpine in ambulatory and hospitalized geriatric psychotics, Ann. New York Acad. Sc. **61**: 72–77, 1955.

[8] Bleuler, M., and Stoll, W. A.: Clinical use of reserpine in psychiatry: Comparison with chlorpromazine, Ann. New York Acad. Sc. **61**: 167–173, 1955.

patients become quiet, cleanly as to their person, more friendly and cooperative, show interest in their environment, participate in the work and recreational activities of the ward, and many become accessible to psychotherapy and other types of treatment. Delusions and other manifestations of their psychosis often persist in less disturbing form or they may disappear in varying degree. In some cases, virtually only sedation was obtained. In this series treatment was continued for from three months (minimal effective period) to nine months, but with a substantial reduction in dosage which again had to be adjusted to the needs of the individual.

In 14 per cent of this series there was no improvement whatever. Twenty-two per cent were "markedly improved" in that they were suitable for discharge; 38 per cent were "moderately improved," they showed relatively normal behavior, were coöperative and participated in the activities of the hospital; and 26 per cent were only slightly improved, in being perhaps cleanlier, less noisy and violent and easier to manage. ". . . every ward that has used the drug has uniformly reported a marked decrease in the decibel level, an increase in the coöperativeness of the patients and decidedly less need for restraints, isolation and seclusion."

It has also greatly restricted the need for electroshock therapy (EST). Only eight of 100 patients who had received both treatments did better with EST than with reserpine, and in them improvement was not long maintained after EST was stopped. Reserpine treatment eliminated the need for EST in 54 of 80 patients for whom it had been scheduled [8] and since then it has been completely eliminated in this group. A similar experience has been reported from other clinics,[8, 9, 10] in which EST has been greatly reduced or largely abandoned for excited violent patients of this type, although this will probably not prove possible for patients who are primarily depressed.

How long maintenance treatment is necessary is a vitally important point which is still undetermined. In Barsa and Kline's series [6] of 41 patients markedly improved, nine relapsed within eight weeks after treatment was stopped, but they were again controlled by repeating the entire course. The 32 others had maintained their improvement eight weeks to five months after stopping treatment. Bleuler [8] states that their usual period of treatment is two to four weeks. Hollister et al.[9] set the period at three months. They give no figures as to relapses but emphasize that "lasting improvement . . . is dependent not only on how much or how long the drug has been given but also what has happened to the patient while he is on the drug. Thus we regard relapse . . . as a manifestation of our failure to exploit thoroughly the therapeutic opportunity the drug has

[9] Hollister, L. E., et al.: Treatment of chronic schizophrenic reactions with reserpine, Ann. New York Acad. Sc. **61**: 92–100, 1955.

[10] Tasher, D. C., and Chermak, M. W.: The use of reserpine in shock-reversible patients and shock-resistant patients, Ann. New York Acad. Sc. **61**: 108–116, 1955.

provided." Hoffman et al.,[11] after a brief seven weeks period of observation of 108 severely disturbed psychotics of whom 73 per cent were improved, were also impressed by the coöperation secured and the accessibility of the patients. "This drug *demands* that every other therapeutic resource available be used intelligently in further treatment . . . while the burdens of caring for the disturbed are lessened by reserpine, the challenge of providing appropriate additional psychiatric treatment for those no longer disturbed will tax all our ingenuity, skill and resources . . . we must not be content with bringing a drug-induced 'tranquility' to our patients."

Noce et al.[12] in a series of 74 similar cases treated with reserpine observed similar changes in behavior, not merely sedation but a "reorganization of the personality" which makes them accessible to psychotherapy and rehabilitation measures. Regarding their (early) results they are highly enthusiastic—if confirmed by long term studies, "reserpine will be the most important therapeutic development in the history of psychiatry." Most observers, however, are much more restrained. There are limitations, relapses, disagreeable side reactions, and under the best circumstances a residual 15 to 25 per cent of deteriorated cases who are not helped at all.

In general the results do not depend upon the specific psychiatric diagnosis but upon the type of behavioral disturbance. Agitation, excitement, violence, manic states are usually relieved. Pure depression, on the other hand, is usually not improved and may be aggravated, although associated anxiety and agitation may be relieved. The age of the patient has little influence, but duration of the illness does, particularly if over five years. Improvement has occurred, however, in some cases of even longer duration. Even senile psychotics and mentally defective subjects who are badly disturbed may show great improvement in behavior. In one such group of 63 cases, "man-hours of work by psychiatric aids, nurses and doctors in their care decreased an average of 50 per cent."[7] Results in epileptics have been contradictory and on the whole unfavorable. In some cases seizures have appeared or increased in frequency. For the present the use of reserpine should probably be restricted to hospitalized epileptic patients.

Mild side effects are common, but severe ones are rare except on massive doses and almost never a threat to life. Doses increased gradually up to 2 mg. per kilogram per day have been given to refractory cases for periods of a week to a month without toxic effects.[7] Common complaints are nasal stuffiness, with coryza, salivation, and mild degrees of drowsiness, lethargy or "torpor," from which patients can usually be easily aroused. Occasionally there are troublesome dreams. Mild gastrointestinal disturbances are

[11] Hoffman, J. L., and Konchegul, L.: Clinical and psychological observations on psychiatric patients treated with reserpine: A preliminary report, Ann. New York Acad. Sc. 61: 144–149, 1955.

[12] Noce, R. H., Williams, D. B., and Rapaport, W.: Reserpine (serpasil) in the management of the mentally ill and mentally retarded. Preliminary report, J.A.M.A. 156: 821–824, 1954.

common with hypermotility, diarrhea and rarely reactivation of peptic ulcers, but reserpine usually stimulates appetite and increases weight. There is usually some lowering of blood pressure (slight except in hypertensives) and a bradycardia which may result in troublesome orthostatic hypotension. Such disturbances usually subside gradually without interrupting treatment. With massive doses more serious disturbances may occur, particularly often an "extrapyramidal syndrome" having virtually all the features of a severe Parkinson's disease. Thus far all such cases reported have cleared up completely when the dose was reduced, even though vigorous treatment might have been continued for a time in spite of this. Severe mental confusion has been mentioned more rarely as a contraindication for further treatment.

Any discussion of reserpine demands mention of chlorpromazine, which closely resembles reserpine in many of its effects on psychotic patients of this type. In some clinics both drugs have been used in comparative studies,[5, 8, 13] and neither is as yet established as superior to the other. Chlorpromazine produces its effect more quickly, and it is rather more helpful than reserpine in patients who are depressed. It is said to excite a Parkinsonian syndrome less frequently. Chlorpromazine, however, is potentially more toxic. Hepatic injury, sometimes with jaundice, occasionally occurs, and a fatal case with agranulocytosis has just been reported.[14] The development of hypersensitivity has been mentioned. Intramuscular injections, often necessary for a prompt response, cause painful infiltrates which are very troublesome. None of these have been reported with reserpine.

A possible advantage in administering both drugs simultaneously is obvious, and several observers have stated that such trials are underway with encouraging results, both in psychiatric patients [5, 13, 15] and in hypertension.[16]

The status of reserpine in the treatment of psychoneurotic states is poorly defined and much larger and better controlled studies will be necessary to warrant any conclusions. Typical are reports by Drake and Ebaugh [17] (40 patients) and by Smith [18] (50 patients) of its use in small doses in ambulatory office patients. Here too the primary effect is tranquilizing, with relief of agitation, tension and anxiety. Depression was not relieved as a rule and may be aggravated. Increased accessibility to psychotherapy has

[13] Kinross-Wright, V.: Chlorpromazine and reserpine in the treatment of psychoses, Ann. New York Acad. Sc. **61**: 174–182, 1955.

[14] Hodges, H. H., and LaZerta, G. D.: Jaundice and agranulocytosis with fatality following chlorpromazine therapy, J.A.M.A. **158**: 114–116, 1955.

[15] Barsa, J. A., and Kline, N. S.: Combined reserpine-chlorpromazine therapy in disturbed psychotics (preliminary clinical report), Am. J. Psychiat. **111**: 780, 1955.

[16] Eiber, H. B.: Combined chlorpromazine-Rauwolfia serpentina therapy in essential hypertension, J.A.M.A. **158**: 730–731, 1955.

[17] Drake, F. R., and Ebaugh, F. G.: The use of reserpine in office psychiatry: Preliminary report, Ann. New York Acad. Sc. **61**: 198–205, 1955.

[18] Smith, S. K.: The use of reserpine in private psychiatric practice, Ann. New York Acad. Sc. **61**: 206–210, 1955.

been stressed. In patients, ambulant or hospitalized, who are receiving EST for depressive reactions, reserpine relieves much of their fear and often prevents the confusion and excitement that commonly follow such treatments. Improvement on the usual small doses is slow, often notable only after a few weeks. Side effects, especially some lethargy or mild drowsiness, nasal stuffiness, and digestive discomforts, although not serious, are often more disturbing to the patients than is the case in serious psychoses and require a good deal of supportive therapy. Reserpine seems to be especially useful in some cases of hypertension of mild to moderate severity in whom emotional factors are a major cause of the hypertension, but its effect on the mental status of the patient does not depend upon lowering blood pressure. In a substantial number of neurotic patients reserpine appears to be useful, but there are no grounds yet for claiming it effects a cure.

As to the effect of reserpine in the major psychoses, no responsible observer yet claims a cure in the sense of a complete and possibly permanent restoration to normal. Most may be hoped for in the acute cases and those in the earlier stages of a chronic illness, for whom reserpine may make possible the utilization of more fundamental curative measures. In deteriorated cases of long standing chronic illness the conversion of a noisy, confused, agitated and combative individual, naked, incontinent and soiled, into a quiet, reasonably coöperative patient who will clothe and feed himself and care for his person [11] is a gain for which both the family and the hospital staff may be truly thankful. Many patients fail to show such a gain, and some have relapsed. It is not yet known how many can maintain such improvement, with or without maintenance treatment, nor how long. That a substantial number of such hitherto hopeless derelicts, the dregs of the state hospitals, should be lifted up from the very bottom of the pit into a state of tolerable and even quasi-normal behavior is really amazing, even though still far removed from a cure.

The prospective liberation of many hospital beds, the economies made possible in the nursing care of such patients, the elimination of many EST and leukotomies, the quieter and more wholesome atmosphere of the "violent" wards, and the improved morale of the hospital personnel all promise to be of great practical importance. The introduction of these drugs has already initiated an era of intensive investigations which should increase our fundamental knowledge of mental illness and, we may hope, greatly facilitate its treatment.

PAUL W. CLOUGH

REVIEWS

Cardiac Auscultation, Including Audio-Visual Principles. By J. Scott Butterworth, M.D., Maurice R. Chassin, M.D., and Robert McGrath, M.D. 111 pages; 24 × 16 cm. Grune and Stratton, Inc., New York. 1955. Price, $4.50.

Instruction in cardiac auscultation is a difficult task which confronts every bedside teacher. It is also too frequently arduous as far as the student is concerned. The authors of this brief book employ audio-visual principles in their instruction in an effort to add the dimension of seeing to that of hearing.

Included are discussions on the physical principles of sound, origin and modification of heart sounds, and the routine of auscultation of the heart. There is emphasis on the clinical aspects of auscultation, with chapters on variations of heart sounds in health and disease, murmurs, disorders of heart rhythm, and various clinical entities and their auscultatory findings.

The basic material is presented lucidly, and the figures in the introductory chapter are of uniformly high caliber. In the timing of murmurs the authors place little emphasis on the value of pulse variations, either jugular or carotid. These are of great aid in the exact timing of second sounds, gallop sounds, opening snap of mitral stenosis, and auricular sounds. Demonstration by audio-visual technic of carotid and jugular pulse contours facilitates the bedside employment of pulse waves in the timing of cardiac events.

Some cardiologists differ with the expressed opinion that "There are measurable differences of effectiveness between the bell and diaphragm chest pieces but we have not been able to convince ourselves that one type of stethoscopic chest piece is preferable to another, since a great deal depends upon the individual's hearing and experience." The selective transmission of high or low frequency component by the diaphragm or bell and the employment of variable pressures on the chest piece are applied by many with great benefit.

The stethograms used as illustrations are sometimes difficult to interpret because of the absence of sufficient identification of the cardiac events. Simultaneous or superimposed pulse and electrocardiographic tracings would be of great value. It is noted that the stethograms are reproduced from tape recordings.

This book represents a worthwhile and interesting approach to the problem of cardiac auscultation. The employment of audio-visual technic in the instruction of auscultation is of great value and should be more widely applied. It is hoped that this book will provide the necessary stimulus for more effective teaching in medical schools of the basic diagnostic technic of cardiac auscultation.

Leonard Scherlis, M.D.

Neurology. 2nd Ed. (in three volumes). By S. A. Kinnier Wilson, M.A., M.D., D.Sc. (Edin.), F.R.C.P., Formerly Physician, National Hospital, Queen Square; edited by A. Ninian Bruce, F.R.C.P. (Edin.), D.Sc. (Edin.), M.D., F.R.S. (Edin.), Lt.-Col. R.A.M.C., Consulting Physician, Bangour Mental Hospital and St. Andrew's Hospital, Hawick. 2212 pages; 25 × 17 cm. The Williams & Wilkins Co., Baltimore. 1955. Price, $37.50.

This is the second edition of a book which for the past fifteen years has constituted the chief reference work in clinical neurology in the English language. The present edition has been expanded to three volumes but the general tone and plan have remained the same. Both editions were published following the death of the author and both have suffered from lack of complete revision. The first volume

presents the toxic and infectious disorders, the second volume the familial and congenital affections and the third volume the vascular, metabolic, neoplastic, and miscellaneous affections of the nervous system. This work is unequaled as regards presentation of classical clinical neurology. The historical background of the nervous diseases is discussed in considerable detail with complete references to the older literature. Many of the more recent advances have been omitted and the evaluation of the older literature is at times contradictory. The lack of complete evaluation of current advances in neurology detracts considerably from the value of this edition. It still remains the best source of background material in clinical neurology and continues as a memorial to a great neurologist.

The references to the literature for each volume are arranged alphabetically at the end of the volumes. The index for each volume is also present at the end of each volume. This latter arrangement may confuse the uninitiated.

These three volumes should be in the library of anyone seriously interested in the clinical aspects of the nervous system.

CHARLES VAN BUSKIRK

Orientamenti Diagnostici e Terapeutici Attuali Nella Chirurgia della Milza (*Present Diagnostic and Therapeutic Orientation in the Surgery of the Spleen*). By G. BENDANDI. 128 pages; 24.5 × 17 cm. (paper-bound). Edizioni Mediche e Scientifiche, Rome. 1954.

This study is based on the observation of 254 cases of diseases of the spleen, primary or secondary.

The author is Associate Professor of Surgery at the University of Rome, and the statistics are based on the cases operated upon in the hospital of that school.

Following a brief discussion of the pathologic physiology of the spleen, the author discusses the absolute and secondary indications for splenectomy, giving a short description of each condition.

In connection with the diagnostic procedure, the technic of the "splenoportography" is discussed: According to this method an opaque medium (Joduron, an iodine compound) is injected directly into the spleen and then a series of radiographs is taken; the splenic vein, the vena porta and its branches are normally visualized, and it is also possible to study the rate of diffusion of the medium. This technic was described by Abeatici e Campi in 1951 (Acta Radiologica 36: 383, 1951).

The review deals with the technical procedure of the splenectomy and with the physiology of the patient following the operation.

A comprehensive bibliography is given at the end.

This discussion is an important contribution to the study of the problem of "hypersplenism," since the review is not limited to the surgical aspect of the pathology of the spleen.

We found particularly interesting the discussion of "Banti's disease"; this was described in Italy in 1894, and since then there have been innumerable discussions as to whether this is a real entity or a nonspecific syndrome, common to a number of different conditions. These points of view are held in Italy by two different schools, one led by Cesa-Bianchi who, since 1939, has held that this condition has to be considered a nonspecific syndrome, having variable etiology but a common mechanism of vascular dysfunction leading to the parenchymal change and the clinical manifestations.

The other school, led by Di-Guglielmo, considers this condition a pure entity, as described by Banti, characterized by unknown etiology, a chronic and progressive course in three periods (anemic-splenomegalic, pre-ascitic, cirrhotic ascitic), anatomo-histologic picture of fibrosis but with relative preservation of the parenchymal pattern, and curability of the condition by splenectomy if the operation is done during the

first period. According to the latter definition the congestive splenomegalies are excluded from this syndrome and considered as independent entities.

This subject is particularly interesting because this disorder is usually interpreted in this country as a syndrome of varying etiology and not as a specific entity, and the thrombophlebitic splenomegalies are considered in the same category.

G. R.

Adrenal Cortex: Transactions of the Fifth Conference, November 4, 5 and 6, 1953, Princeton, N. J. Edited by ELAINE P. RALLI, M.D., Associate Professor of Medicine, New York University College of Medicine, New York, N. Y. 187 pages; 23.5 × 16 cm. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y. 1954. Price, $3.75.

This book consists of three reports to the conference, with a careful record of the discussions prompted by each paper. The discussions occupy more space than the original papers, and it is clear that the organizers of these conferences have achieved their purpose in bringing together interested workers from many disciplines and stimulating them to an interchange of ideas on a subject to which they had all contributed.

The framework for these discussions was furnished by papers on the isolation and partial identification of the salt and water factor of the adrenal cortex, now known as aldosterone, by H. L. Mason; the metabolism of adrenal steroids, by Ralph I. Dorfman; and a review and presentation of original work by Frank G. Young on the question of the unity of ACTH.

The papers presented are, of necessity, incomplete, as they represent reports of work in progress in an exceedingly complex field. The major value of this volume is as an indicator of the trend of thought of a number of gifted investigators. It is highly recommended for those who are actively investigating the physiology and chemistry of the adrenal cortex, and to the advanced student who is quite familiar with the terminology of the subject.

S. P. B.

Tumors of the Retroperitoneum, Mesentery and Peritoneum. Atlas of Tumor Pathology, Section VI—Fascicles 23 and 24. By LAUREN V. ACKERMAN, M.D., Professor of Pathology and Surgical Pathology, Washington University School of Medicine, St. Louis, Missouri. 136 pages; 20 × 26 cm. (paper-bound). Published by the Armed Forces Institute of Pathology, under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington 25, D. C. 1954. Price, $1.50.

This book is an atlas of tumors which arise primarily from tissues and organs of the retroperitoneal space, mesentery and peritoneum. These tumors are classified in a usable manner as to benignity, malignancy, and tissue of origin. Neurogenous tumors, tumors arising from heterotopic adrenal cortical tissue, and teratomas are excellently portrayed. Rare primary tumors of the mesentery and omentum are discussed. Mesothelioma and metastatic lesions of the peritoneum are thoroughly covered. A brief but adequate gross and microscopic description is given of each tumor, and numerous references to illustrations aid greatly in studying the unusual neoplasms covered by this work. Large, clear, well-chosen illustrations of gross lesions and photomicrographs make this volume particularly valuable. A thorough, up to date bibliography accompanies each section. This atlas should appeal to pathologists and advanced students of pathology.

C. F. C.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Adrenal Function in Infants and Children: Report of the Thirteenth M & R Pediatric Research Conference. 104 pages; 23 × 15 cm. (paper-bound). 1955. M & R Laboratories, Columbus, Ohio. Price: Available to the medical profession without charge.

Ageing: General Aspects. Ciba Foundation Colloquia on Ageing. Volume I. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and MARGARET P. CAMERON, M.A., A.B.L.S., assisted by JOAN ETHERINGTON. 255 pages; 21 × 14 cm. 1955. Little, Brown and Company, Boston. Price, $6.75.

Annotated Bibliography of Vitamin E, 1952–1954. Volume III. Compiled by PHILIP L. HARRIS and WILMA KUJAWSKI, of The Research Laboratories of Distillation Products Industries, Rochester, New York. 182 pages; 27.5 × 21 cm. (paper-bound). 1955. Distributed by The National Vitamin Foundation, Inc., New York. Price, $3.00.

Collected Papers of the Mayo Clinic and the Mayo Foundation. Volume XLVI, 1954. Edited by RICHARD M. HEWITT, B.A., M.A., M.D., A. B. NEVLING, M.D., JOHN R. MINER, B.A., Sc.D., JAMES R. ECKMAN, A.B., M.A., Ph.D., M. KATHARINE SMITH, B.A., CARL M. GAMBILL, A.B., M.D., M.P.H., FLORENCE SCHMIDT, B.S.E., and GEORGE G. STILWELL, A.B., M.D. 843 pages; 24 × 15.5 cm. 1955. W. B. Saunders Company, Philadelphia. Price, $12.50.

Differential Diagnosis: The Interpretation of Clinical Evidence. By A. MCGEHEE HARVEY, M.D., Professor of Medicine and Head of the Department of Internal Medicine, The Johns Hopkins University School of Medicine, etc.; and JAMES BORDLEY, III, M.D., Director, Mary Imogene Bassett Hospital, Cooperstown, N. Y., etc. 665 pages; 24 × 16 cm. 1955. W. B. Saunders Company, Philadelphia. Price, $11.00.

The Genesis and Prevention of Cancer. 2nd Ed. By W. SAMPSON HANDLEY, M.S. Lond., F.R.C.S., Vice-President of the Royal College of Surgeons of England, 1931–33, etc. 320 pages; 21.5 × 14 cm. 1955. The Macmillan Company, New York. Price, $4.00.

L'Hérédité en Médecine: Caractères, Maladies, Corrélations. By A. TOURAINE. 875 pages; 25 × 17 cm. 1955. Masson et Cie, Paris. Price, Broché: 6,400 fr.; cartonné toile: 7,200 fr.

Pathology for the Surgeon. 7th Ed. By WILLIAM BOYD, M.D., Edin., Dipl. Psychiat. Edin., F.R.C.S. Canada, F.R.C.P. Lond., M.R.C.P. Edin., F.R.S. Canada, LL.D. Sask., D.Sc. Man., M.D. Oslo, Lecturer on the Humanities in Medicine, The University of Toronto, etc. 737 pages; 26 × 18 cm. 1955. W. B. Saunders Company, Philadelphia. Price, $12.50.

The Practice of Dynamic Psychiatry. By JULES H. MASSERMAN, M.D., Professor of Neurology and Psychiatry, Northwestern University, Chicago, Illinois. 790 pages; 24 × 16 cm. 1955. W. B. Saunders Company, Philadelphia. Price, $12.00.

Problems of Consciousness: Transactions of the Fifth Conference, March 22, 23 and 24, 1954, Princeton, N. J. Edited by HAROLD A. ABRAMSON, M.D., Assistant Clinical Professor of Physiology, Columbia University College of Physicians and Surgeons, etc. 180 pages; 23.5 × 15.5 cm. 1955. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y. Price, $3.50.

The Rural Hospital: Its Structure and Organization. By DR. R. F. BRIDGMAN, Deputy Director of Health of the Department of the Seine, France, etc. 162 pages; 24 × 16 cm. (paper-bound). 1955. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, New York. Price, $4.00 (cloth-bound).

Secretion of Adrenaline and Sympathins. By Y. SATAKE, Professor of Physiology, Emeritus, The Tohoku University, etc. 158 pages; 26.5 × 18.5 cm. 1955. Nanzando Co., Ltd., Hongo, Tokyo, Japan. Price, $4.00.

Surgical Forum: Proceedings of the Forum Sessions, Fortieth Clinical Congress of The American College of Surgeons, Atlantic City, N. J., November, 1954. COMMITTEE ON FORUM ON FUNDAMENTAL SURGICAL PROBLEMS: HARRIS B. SHUMACKER, JR., M.D., F.A.C.S., Indianapolis, Chairman; J. GARROTT ALLEN, M.D., F.A.C.S., Chicago; BRADFORD CANNON, M.D., F.A.C.S., Boston; WARREN H. COLE, M.D., F.A.C.S., Chicago; ROBERT E. GROSS, M.D., F.A.C.S., Boston; J. ALBERT KEY, M.D., F.A.C.S., St. Louis; C. HUNTER SHELDEN, M.D., F.A.C.S., Pasadena; HOWARD C. TAYLOR, JR., M.D., F.A.C.S., New York; and SAMUEL A. VEST, M.D., F.A.C.S., Charlottesville. 851 pages; 25.5 × 16.5 cm. 1955. W. B. Saunders Company, Philadelphia. Price, $10.00.

A Textbook of Medicine. 9th Ed. Edited by RUSSELL L. CECIL, M.D., Sc.D., Professor of Clinical Medicine Emeritus, Cornell University, New York; and ROBERT F. LOEB, M.D., Sc.D., D. Hon. Causa., LL.D., Bard Professor of Medicine, Columbia University, New York; Associate Editors: ALEXANDER B. GUTMAN, M.D., Ph.D., Professor of Medicine, Columbia University, New York; WALSH MCDERMOTT, M.D., Livingston Farrand Professor of Public Health and Preventive Medicine, Cornell University, New York; and HAROLD G. WOLFF, M.D., Professor of Medicine (Neurology), Cornell University, New York. 1,786 pages; 26 × 18.5 cm. 1955. W. B. Saunders Company, Philadelphia. Price, $15.00.

Veterans Administration Technical Bulletins, Series 10, Volume VII, 1954. Pages not numbered; 27 × 20.5 cm. 1955. Veterans Administration, Washington. Not for sale—limited edition for distribution to VA hospitals and medical libraries.